Inter Partes Reexamination No. 95/001,096
Declaration of Campbell Rogers, M.D.
Exhibit 91

Evaluation of a High-Dose *Dexamethasone*-Eluting Stent

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This study evaluated the safety and efficacy of a dexamethasone-eluting stent with a special high dexamethasone-loading dose for treatment of de novo coronary lesions in 30 patients. Eight patients had in-stent restenosis (restenosis rate 31%) at 6-month follow-up, and the in-stent late lumen loss was 0.96 ± 0.63 mm due to an average intimal hyperplasia area obstruction of 32 ± 21%, indicating that high-dose dexamethasone-loaded stents do not significantly reduce neointimal proliferation. ©2004 by Excerpta Medica, Inc.

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The purpose of this pilot study of 30 patients was to evaluate whether a phosphorylcholine-coated stent loaded with a special high dose of dexamethasone is safe and results in a low late lumen loss and low restenosis rate after treatment of de novo lesions in human coronary arteries. A large randomized study (the Evaluation of 9α-F-16-Methylvednisolon Eluting Stents on the Reduction of Restenosis [EMPEROR] trial) was believed to follow after successful termination of the pilot study, but it was halted before patient inclusion due to the results of this pilot study.

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Thirty consecutive symptomatic patients with native coronary lesions (>50% diameter stenosis) treated at the University Clinic Aachen (Aachen, Germany) were included in the study. Inclusion criteria were lesion length to be covered by one 18-mm-long stent, and a vessel diameter between 2.75 and 3.75 mm. Patients had to have 1-vessel disease. Criteria for exclusion were an ejection fraction <30%, unprotected left main location, heavy calcification, excessive tortuousity of the proximal vessel, a life expectancy of <1 year, myocardial infarction within the previous 72 hours, and previous intracoronary brachytherapy. All patients gave written informed consent. The protocol was approved by the ethics committee of the University Aachen.

Direct stenting for treatment of in-stent restenosis was allowed. In cases of predilatation before stent placement, use of a balloon shorter than the stent was encouraged. The stent used in the study was a Bio*divYsio* Matrix Lo phosphorylchlorine-coated stent (Abbott Vascular Devices, Redwood City, California) of 18-mm length in diameters of 2.75, 3.0, and 3.5 mm, which was loaded with a special high dose of dexamethasone (Abbott Vascular Devices). During the interventional procedure, heparin was administered according to standard practice. Aspirin (100 mg/day) and therapy with clopidogrel (300-mg loading dose) was begun before the procedure. After the procedure, in addition to aspirin, clopidogrel (75 mg/day) was administered for 3 months.

The Bio*divYsio* Matrix Lo phosphorylchlorine-coated stent is a conventional stainless steel stent. The phosphorylcholine coating is 2-μm thick on the side of the stent, which comes in contact with the vessel wall; the coating is designed to act as a depot for drugs (Figure 1). The coating swells as the drug is incorporated. The stent was bathed in dexamethasone solution with a concentration of 15 mg/ml and subsequently pipette loaded with dexamethasone. This process allowed loading of a dose density of 2.2 $\mu g\ mm^2$ to the abluminal surface of the stents. The total dexamethasone dose achieved for the 18-mm-long stents was 225 μg. Preclinical studies have confirmed release and persistance of dexamethasone in tissue specimen for several days after implantation of a dexamethasone-eluting stent.

Procedural success was defined as a <30% final diameter stenosis in the treated lesion and the absence of major clinical complications (in-hospital death, Q-wave myocardial infarction, or emergency coronary bypass surgery). All patients were monitored for 6 months after the procedure for any major adverse cardiac event (MACE), defined as death, myocardial infarction, or need for target vessel revascularization. Baseline clinical demographics, in-hospital complications, and the occurrence of death, myocardial infarction, and late target vessel revascularization during follow-up were verified by independent hospital chart review and source documentation.

Procedural and follow-up angiograms were analyzed according to previously published methods by an independent core laboratory (Brigham & Women's Hospital, Boston, Massachusetts). Quantitative angiographic analysis was performed using an automated edge-detection algorithm (Medis CMS, Leiden, The Netherlands). Standard quantitative characteristics included proximal and distal references, lesion length, and minimal luminal diameter before and after the procedure and at follow-up. After the procedure and at follow-up, the minimal luminal diameter was determined for the target lesion, defined as the in-stent segment plus the proximal and distal

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TABLE 1 Patients' Baseline Demographic, Lesion, and Procedural Characteristics (n = 30)

Age (yrs)	63 ± 11
Men	22 (73%)
Diabetes mellitus	5 (17%)
Hypercholesterolemia*	18 (60%)
Systemic hypertension	20 (67%)
Smokers	18 (60%)
Unstable angina pectoris	3 (10%)
Previous myocardial infarction	13 (43%)
Previous coronary angioplasty	4 (13%)
No. of narrowed coronary arteries	
1	18 (60%)
2	11 (37%)
3	1 (3%)
Treated coronary arteries	
Left anterior descending	6 (20%)
Left circumflex	9 (30%)
Right	15 (50%)
Lesion classification	
A (%)	0
B1 (%)	12 (40%)
B2 (%)	18 (60%)
C (%)	0
Lesion length (mm)	15 ± 6
Implanted dexamethasone-eluting stent diameter (mm)	
2.75	(9 stents)
3.00	(12 stents)
3.50	(9 stents)

*Hypercholesterolemia is defined as serum cholesterol levels >240 mg/dl or patients medically treated.

TABLE 2 Quantitative Coronary Angiographic Data

Reference diameter	
Before procedure (mm)	2.83 ± 0.59
After procedure (mm)	2.86 ± 0.58
Follow-up (mm)	2.78 ± 0.59
Minimal lumen diameter	
Preprocedure (mm)	0.89 ± 0.26
Postprocedure (in-stent) (mm)	2.61 ± 0.43
Postprocedure (in-lesions) (mm)	2.13 ± 0.53
Follow-up (in-stent) (mm)	1.57 ± 0.68
Follow-up (in-lesion) (mm)	1.53 ± 0.65
Diameter stenosis	
Preprocedure (%)	69 ± 8
Postprocedure (%)	11 ± 10
Follow-up (in-stent) (%)	43 ± 22
Follow-up (in-lesion) (%)	45 ± 20
Acute gain (mm)	1.64 ± 0.34
In-stent late loss (mm)	0.96 ± 0.63
In-lesion late loss (mm)	0.80 ± 0.64
Restenosis	8 (31%)

5-mm edge segments (in-lesion), and for the stented segment without adjacent edge segments. Late loss was calculated as the difference between minimal lumen diameter after the procedure and that at follow-up. Angiographic restenosis was defined as a >50% diameter stenosis within the target lesion.

Automatic pull-back intravascular ultrasound images were obtained at follow-up angiography. The coronary analysis segment started 5 mm distal and extended 5 mm proximal to the implanted stent. Intravascular ultrasound images were analyzed by an independent core laboratory at the University Aachen. Luminal, stent, vessel, and neointimal cross-sectional areas were determined at 1-mm increments and average areas were calculated over the total stent length.

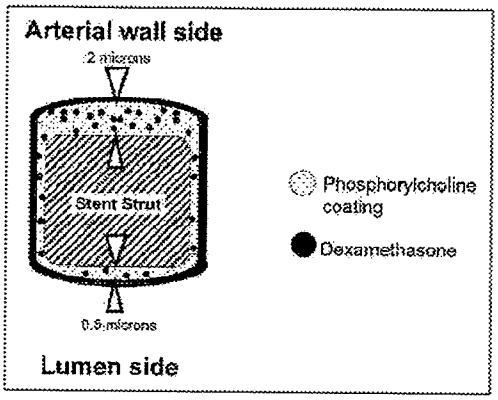

FIGURE 1. Dexamethasone-eluting stent design. The stent strut is covered with a phosphorylcholine coating that is 2-μm thick on the arterial wall side. Dexamethasone is loaded into the phosphorylcholine coating and there is an additional dexamethasone layer on the phosphorylcholine coating.

Continuous variables are reported as mean ± SD. Dichotomous variables are reported as percentages. Comparison between postprocedure and 6-month follow-up measurements was performed with a 2-tailed paired *t* test. A p value <0.05 was considered statistically significant.

Thirty patients (63 ± 11 years; 22 men) were included in the study. Baseline demographic characteristics are listed in Table 1. In each patient, 1 coronary lesion was treated with a dexamethasone-eluting stent.

Lesion characteristics are listed in Table 1. In 19 lesions, predilatation before implantation of a dexamethasone-eluting stent was performed. In 11 lesions, direct stenting within the in-stent restenosis was achieved. The decision to use direct stenting was made by the implanting physician based on the vessel anatomy. A conservative approach was taken with zero failures to cross the lesion in either direct stenting or stenting with predilatation. There was 100% procedural success. No subacute stent thrombosis occurred. At 30 days, the MACE rate was 0%. During the 6-month follow-up, 1 patient had a MACE (3.3%). This patient had recurrent chest pain due to diffuse in-stent restenosis and underwent repeat angioplasty at the target lesion. No patient died and none had myocardial infarction.

Of the 30 patients, 26 (87%) underwent 6-month follow-up angiography. Binary restenosis was documented in 8 lesions (31%). Average lesion length at follow-up was 16.6 ± 7.5 mm. Six lesions had diffuse in-stent restenosis, in 2 lesions there was focal restenosis. Quantitative coronary angiographic data are listed in Table 2. In-stent diameter stenosis at follow-up was 43 ± 22% (−7% to 93%), and average in-stent late loss was 0.97 ± 0.63 mm (Figure 2). Intravascular ultrasound was performed at follow-up in 18 lesions. The average intimal hyperplasia cross-sectional area was 2.45 ± 1.61 mm^2 within a mean stent cross-sectional area of 7.95 ± 2.43 mm^2. Percent

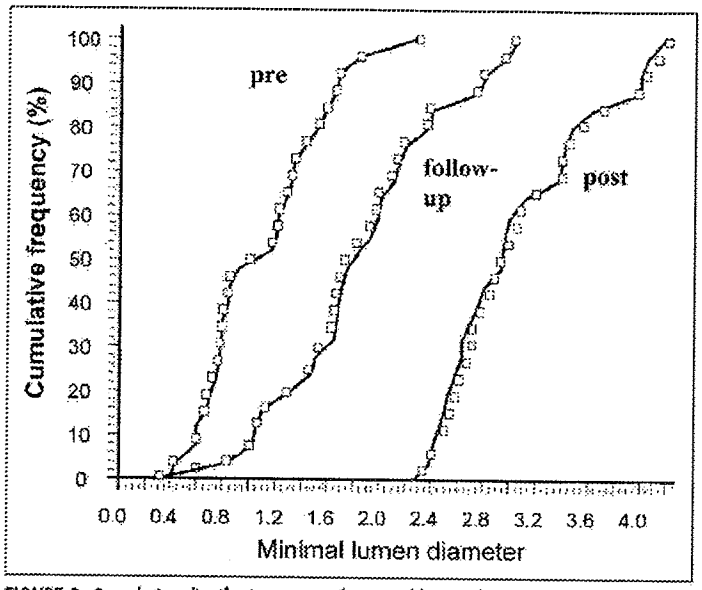

FIGURE 2. Cumulative distribution curve of minimal lumen diameter.

area obstruction was 32 ± 21%. There was no sign of significant incomplete stent apposition.

Subgroup analysis for lesions treated with direct placement of a dexamethasone-eluting stent was performed to determine the effect of a potentially avoided geographic miss. In these 11 lesions, the in-stent late loss was 1.06 ± 0.72 mm and the in-stent minimal lumen diameter at follow-up was 1.74 ± 0.85 mm.

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The results of this study do not support the hypothesis that a special high-dose dexamethasone-eluting stent reduces late lumen loss and restenosis.

Histologic scores for the inflammatory response after stent implantation have been tightly correlated with neointimal thickness and restenosis.[1] Because of their wide range of anti-inflammatory effects, glucocorticoids have attracted interest as a potential modality to suppress restenosis after coronary interventions. Early in vitro studies have reported that different corticosteroid agents inhibit the proliferation of lesion-derived smooth muscle cells by up to 70% to 80%[2,3] by decreasing the sensitivity to mitogenic stimulation by serum or high-density lipoproteins. Clinical trials on the use of systemic pulse applications, as well as systemic pulse application followed by a short period of glucocorticoid administration, have been performed after balloon angioplasty as well as after stent implantation. No effect of glucocorticoid administration on the frequency of restenosis was shown in these studies.[4–6] The failure to reduce restenosis was attributed to an insufficient local effect, as well as the nonfasting effect of a pulse application. However, systemic treatment with prednisone was recently found to be effective in reducing clinical events after stent implantation in selected patients with elevated C-reactive protein.[7] The availability of drug coatings able to deliver high doses of a drug over a prolonged period of time has given new perspective to the use of glucocorticoids for suppression of the restenosis process.[8–11] A previous pilot trial (Study of antirestenosis with the Biodivysio dexamethasone-eluting stent [STRIDE]) on the use of a stent loaded with a lower dose of dexamethasone (0.44 $\mu g/mm^2$) was promising because the restenosis rate was only 13.3%.[12] However, patients whose conditions are known to be associated with a high restenosis rate, such as diabetics, were excluded from the trial. In contrast, the results of this study indicate that restenosis after implantation of a high-dose dexamethasone-eluting stent is similar to levels reported for bare metal or non–drug-loaded Biodivysio phosphorylcholine-coated stents.[13–15]

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A Multicenter, Randomized Trial of Coronary Angioplasty Versus Directional Atherectomy for Patients With Saphenous Vein Bypass Graft Lesions

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Background Directional coronary atherectomy and percutaneous transluminal coronary angioplasty have both been used in symptomatic patients with coronary saphenous vein bypass graft stenoses. The relative merits of plaque excision and removal versus balloon dilatation remain uncertain. We compared outcomes after directional coronary atherectomy or angioplasty in patients with de novo bypass graft stenoses.

Methods and Results Fifty-four North American and European sites randomized 305 patients with de novo vein graft lesions to atherectomy (n=149) or angioplasty (n=156). Quantitative coronary angiography at a core laboratory assessed initial and 6-month results. Initial angiographic success was greater with atherectomy (89.2% versus 79.0%), as was initial luminal gain (1.45 versus 1.12 mm, $P<.001$). Distal embolization was increased with atherectomy ($P=.012$), and a trend was shown toward more non–Q-wave myocardial infarction ($P=.09$). Although the 6-month net minimum luminal diameter gain was 0.68 mm for atherectomy and 0.50 mm for angioplasty, the restenosis rates were similar, 45.6% for atherectomy and 50.5% for angioplasty ($P=.491$). At 6 months, there was a trend toward decreased repeated target-vessel interventions for atherectomy ($P=.092$); in addition, 13.2% of patients treated with atherectomy versus 22.4% of the angioplasty patients ($P=.041$) required repeated percutaneous intervention of the initial target lesion.

Conclusions Atherectomy of de novo vein graft lesions was associated with improved initial angiographic success and luminal diameter but also with increased distal embolization. There was no difference in 6-month restenosis rates, although primary atherectomy patients tended to require fewer target-vessel revascularization procedures. (***Circulation. 1995;91:1966-1974.***)

Key Words • angioplasty • revascularization

Treatment of patients with coronary artery bypass graft stenoses constitutes an increasingly large part of the practice of interventional cardiology.[1-8] Percutaneous transluminal coronary angioplasty (PTCA) has been relatively widely used, but the clinical outcomes have varied, depending on the age of the graft, the location of the stenosis within the graft, and the specific anatomic features.[1-8,9,10] Restenosis rates in grafted vessels are markedly higher than those in native vessels, particularly in older grafts (≥3 years old) and in stenoses involving the aortic ostium or graft body. In addition to restenosis, embolization of atheromatous or thrombotic material during the procedure has been reported in up to 5% of patients.

Directional coronary atherectomy (DCA) has also been used to treat these patients.[7,8,11-16] In the initial Devices for Vascular Intervention (DVI) Registry (Redwood City, Calif), 17% of procedures involved saphenous vein bypass grafts. Observational studies of DCA have reported restenosis rates of approximately 40% for de novo vein graft lesions.[7,13-15] A decrease in restenosis rates could theoretically be achieved by debulking the lesion rather than through dilatation alone. The hypothesis of this randomized, multicenter trial was that atherectomy would result in lower restenosis rates than conventional angioplasty in patients with de novo vein graft stenoses.

Methods

Study Sites and Operators

Fifty-four experienced centers enrolled patients (52 in North America and 2 in Europe; see the Appendix). These centers and investigators were selected because they had experience with both coronary atherectomy and angioplasty and had a background of clinical investigation in interventional cardiology.[17] To qualify as investigators, individual operators had to

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From the Mayo Foundation, Rochester, Minn (D.R.H., P.B.B.); the Cleveland (Ohio) Clinic Foundation (E.J.T., P.L.W., S.G.E.); Duke University Medical Center, Durham, NC (R.M.C., L.G.B., K.L.L., G.P.K.); Loyola Medical Center, Chicago, Ill (F.L.); William Beaumont–Royal Oak Hospital, Royal Oak, Mich (R.S.); the University of Louisville, Ky (J.D.T.); Maine Medical Center, Portland (M.A.K.); Maimonides Medical Center, Brooklyn, NY (J.S.); Graduate Hospital, Philadelphia, Pa (R.S.G.); Toronto (Ontario) General Hospital (A.G.A.); and St Vincent's Hospital, Indianapolis, Ind (C.A.P.).

A complete list of investigators and centers is provided in the Appendix.

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TABLE 1. Summary of Nonprotocol Procedures

Reason for Exclusion	n (%)
Investigator preference not to randomize	141 (36)
Patient received PTCA	43 (11)
Patient received Stent	8 (2)
Patient received DCA	4 (1)
Unknown procedure	86 (22)
Restenotic lesion	76 (19)
Participation in other study that precluded enrollment in CAVEAT-II	39 (10)
Patient refusal	28 (7)
Other graft lesions unsuitable for DCA	24 (6)
PI not available for procedure	22 (5)
Other	18 (4)
Myocardial infarction within 5 days of procedure	15 (4)
Too small for DCA	13 (3)
100% occlusion	10 (3)
Lesion length >12 mm	8 (2)
Lesion stenosis <60%	2 (1)
Total	396 (100)

PTCA indicates percutaneous transluminal coronary angioplasty; DCA, directional coronary atherectomy; and PI, principal investigator.

have performed more than 400 angioplasty procedures with a success rate exceeding 85% and more than 50 DCA procedures with a success rate exceeding 80%. At each site, the Institutional Review Board approved the protocol.

Patient Selection

Patients with prior coronary bypass surgery and de novo vein graft lesions who required revascularization and were suitable for either DCA or PTCA were considered for enrollment. The angiographic inclusion criteria were (1) de novo vein graft lesion; (2) vein graft suitable for ≥6F atherectomy catheter (≥3.0 mm); (3) a subtotal diameter stenosis ≥60% and <100% by visual assessment; and (4) lesion length ≤12 mm. If more than one lesion was present in the vein graft, all had to be amenable to either technique to conform with a single treatment assignment. Patients who had had a myocardial infarction within the previous 5 days were excluded. A log of each atherectomy performed on a vein graft outside of CAVEAT-II was maintained at each site (Table 1). The reasons for not including patients in CAVEAT-II varied, although the most common reason was investigator preference, which occurred in only 36% of the patients. Participation in another investigational study and repeated treatment of lesions were the reasons for exclusion in 10% and 19% of the patients, respectively.

Randomization

The coordinating center was Duke University in Durham, NC. After informed consent was obtained, the randomization center was contacted by telephone for treatment assignment.

Revascularization Procedures

Procedural technical details were published previously for atherectomy and PTCA.[17-19] Although technical success was defined conventionally as achieving ≤50% stenosis, the goal of revascularization was to achieve an angiographic result of the minimum possible residual stenosis (<20% residual stenosis). Crossover to the other treatment modality was strongly discouraged, but predilatation with a ≤2.0-mm balloon was permitted before atherectomy. The operators prospectively identified patients in whom predilatation would be needed; this was not considered crossover.

Aspirin (≥160 mg) and at least one dose of a calcium channel blocker were administered within 24 hours before the procedure. Activated clotting times were maintained at >350 seconds during the procedure by administering a 10 000-U bolus of heparin; supplemental boluses were given, depending on the size of the patient and the length of the procedure. Femoral access sheaths were removed 4 to 24 hours after the procedure was completed. After the procedure, aspirin (325 mg q.d.) and a calcium channel blocker were given for approximately 1 month. Warfarin was not routinely administered. ECGs were obtained before and within 24 hours after the procedure. Creatine kinase levels with myocardial isoenzymes (MB) were obtained 12 and 24 hours after the procedure.

Angiography

At the beginning of each procedure, after a dose of 100 to 200 mcg of intracoronary nitroglycerin, coronary angiography was obtained of the target graft in two orthogonal views with a 7F or an 8F diagnostic coronary arterial catheter. These views were repeated at the end of the procedure, again with a 7F or an 8F catheter. This procedure was repeated for the 6-month follow-up angiogram.

The Cleveland Clinic Foundation Angiographic Core Laboratory performed independent, blinded assessment by use of quantitative coronary angiography (QCA) (Image Com). Paired acute and follow-up angiograms were measured by technicians blinded to treatment assignment; the device-containing images were spliced out. The most severe hemiaxial end-diastolic view without foreshortening was used for analysis, although both orthogonal views were analyzed. Preprocedure films were analyzed for extent of coronary artery disease, number of lesions, and lesion complexity and morphology. Each lesion was assessed in all films for vessel caliber, absolute minimum diameter, percent diameter stenosis, and percent stenosis by cross-sectional area.

Quantitative analysis was performed with the use of a validated edge-detection algorithm.[20] Vessel edges were determined with the computerized algorithm, and luminal diameters were measured with the empty and contrast-filled catheters as references.

The long-term interobserver variability of the Angiographic Core Laboratory was determined by analyzing 15 cineangiograms on two occasions 8 months apart. Each reviewer independently selected projection angle and frame selection. Standard errors (and correlation coefficient, r) of the measurements for reference diameter and minimum luminal diameter values were 0.25 (.89) and 0.18 (.81) preintervention and 0.23 (.91) and 0.16 (.97) postintervention.

Core Pathology Laboratory

St Elizabeth's Hospital (Boston, Mass) served as the core pathology laboratory. Tissue specimens from atherectomy were immediately placed in 4% paraformaldehyde/PBS for 2 hours, stored at 4°C in 30% sucrose/phosphate-buffered saline, and sent to the core laboratory for light microscopy and immunohistochemistry.

End Points

Acute end points included procedural success (≤50% diameter stenosis by QCA), major complications, a composite index of complications (death, myocardial infarction, emergency bypass, or abrupt-closure syndrome), abrupt closure, hospital charges, quality of life, and length of hospital stay. The diagnosis of myocardial infarction by each site was defined as creatine kinase MB greater than twice the upper limit of normal. Q-wave changes were recorded. Abrupt closure was defined by the site as angiographically documented Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow with 100% stenosis and clinical or ECG evidence of ischemia lasting >5 minutes. Distal embolization was defined according to the clinical judgment of the individual investigators and included decreased flow in a previously patent vessel distal to the target lesion in the absence of an occlusion at the treatment site.

End points assessed during follow-up included restenosis (by absolute luminal diameter), major late clinical events (death, myocardial infarction, and coronary bypass surgery), functional capacity, and exercise time. Other follow-up events included

TABLE 2. Baseline Clinical Characteristics

	DCA, n=149	PTCA, n=156
Age, y	65.5 (58, 71)	65 (58, 71)
Male sex	123 (82.6%)	132 (84.6)
Height, cm	170.2 (166.5, 176.5)	172.7 (166.7, 178.0)
Weight, kg	81.8 (74.0, 9.0)	81.0 (71.8, 92.2)
Hypertension	95 (63.8)	94 (60.3)
Diabetes mellitus	54 (36.2)	51 (32.7)
Hypercholesterolemia	87 (59.2)	91 (59.5)
Current smoker	33 (22.2)	22 (14.1)
Prior myocardial infarction	109 (73.2)	98 (62.8)
Myocardial infarction within 14 days	20 (13.4)	17 (10.9)
Peripheral vascular disease	39 (26.2)	24 (15.4)
Cerebrovascular disease	21 (14.1)	18 (11.5)
Renal insufficiency	12 (8.1)	12 (7.7)
Chronic lung disease	12 (8.1)	6 (3.8)
Unstable angina	133 (89.3)	138 (88.5)
Canadian Heart Class angina		
I	5 (3.4)	5 (3.2)
II	24 (16.1)	19 (12.2)
III or IV	120 (8.5)	132 (84.6)
Congestive heart failure	23 (15.4)	21 (13.5)
Class 3 or 4	13 (8.7)	9 (5.8)
Any comorbid condition	55 (36.9)	43 (27.6)

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty. Values are median (25th, 75th percentiles) or number (%) of patients in each category.

angina pectoris; need for repeated intervention; and a composite index of death, myocardial infarction, coronary bypass graft surgery, and repeated intervention.

Determination of Sample Size

The sample size calculation was based on the assumption that the restenosis rate after angioplasty would be approximately 60% compared with approximately 40% after atherectomy.[1,5,10,13] It was assumed that 15% of patients would have an unsuccessful procedure or crossover, and 15% would not return for angiographic follow-up. Given these assumptions and using an α of .05 and 80% power, we estimated that 300 patients would be required.

Data Management and Statistical Analysis

The research coordinator and investigators prospectively entered the data on a case report form at each site.[17] These case report forms were forwarded to the coordinating center and verified by range and consistency checks. Cardiology nurse monitors audited all case report forms. Continuous data are presented as median (25th, 75th percentiles); to test for a difference between treatment groups, we used the Wilcoxon rank-sum test.[21] Categorical data are presented as frequency (percentage); we used the χ^2 test or Fisher's Exact Test when comparing treatment groups. Kaplan-Meier survival methods were used to determine the 6-month event rates for clinical outcomes. The event rates were compared between treatment groups using the log-rank test, which incorporated data from a follow-up window that extended through 240 days after enrollment.

Patients with missing data for a given variable were excluded from the calculation of the percentage of patients having that characteristic. This prevented the addition of bias that would result from assuming that patients with missing data were negative for that characteristic.

Relation With Sponsors

The Steering Committee set standards for protocol design and execution that were independent of the sponsors (DVI and Eli Lilly Inc). No member of the Steering Committee or coordinating center was permitted to have any financial equity position with either sponsor. All data were managed at the Duke University Coordinating Center, and no data were accessible to the investigators or sponsors until all 6-month follow-up angiographic data had been analyzed.

Results

From March 12, 1992, to April 16, 1993, 305 patients were randomized: 149 to DCA and 156 to PTCA (Table 2). The majority of patients had unstable angina. Comorbid conditions were frequent; they were seen in 36.9% of the DCA patients and 27.6% of PTCA patients. Rates of infarction within 14 days, congestive heart failure, and cerebrovascular disease were similar in both groups, although peripheral vascular disease occurred more frequently in the DCA group (26.2% versus 15.4%). The grafts being treated were old: 9.5 years old for DCA and 9.9 years old for PTCA (Table 3).

The distributions of vein graft locations and locations of the stenoses within the grafts were similar between the two groups; grafts with single distal insertion sites were most commonly treated. In the DCA patients, a vein graft to the circumflex was most common, while in the PTCA group, an equal number of left anterior descending and circumflex coronary grafts were treated. Typically, the lesion was within the body of the graft (81.9% for DCA; 89.1% for PTCA); only a minority of patients had aorto-ostial lesions treated (14.8% and 9.0% for DCA and PTCA, respectively). As per the protocol, the initial TIMI grade flow of 2 or 3 was predominant in each group (89.5% for DCA; 92.7% for PTCA). A small percentage of patients had decreased flow at baseline.

There was no difference in lesion length between the DCA (10.9 mm) and PTCA (11.0 mm) groups. Adverse specific lesion morphology was common and similar in the two groups (Table 4). Lesion eccentricity was the most

TABLE 3. Angiographic Characteristics

	DCA, n=149	PTCA, n=156
Age of grafts, y	9.5 (6.8, 12.4)	9.9 (7.0, 11.6)
Ejection fraction	52 (45, 60)	50 (44, 60)
Native vessel supplied		
Left anterior descending artery	45 (30.2)	55 (35.3)
Right coronary artery	38 (25.5)	42 (26.9)
Circumflex artery	62 (41.6)	55 (35.3)
≥1 vessel	4 (2.7)	7 (4.5)
Type of graft to be treated		
Single SVG	131 (88.5)	127 (81.9)
Sequential SVG	14 (9.5)	21 (13.6)
Y-type SVG	3 (2.0)	7 (4.5)
Target lesion location*		
Aortic anastomosis	22 (14.8)	14 (9.0)
Proximal third graft body	42 (28.2)	57 (36.5)
Middle third graft body	57 (38.3)	52 (33.3)
Distal third graft body	28 (18.8)	43 (27.6)
Coronary anastomosis	8 (5.4)	7 (4.5)
Number of lesions in target graft		
1	130 (89.0)	129 (83.7)
2	14 (9.6)	23 (14.9)
3	2 (1.4)	2 (1.3)
Initial TIMI grade flow		
0 or 1	15 (10.5)	11 (7.3)
2	47 (32.9)	36 (24.0)
3	81 (56.6)	103 (68.7)
Lesion length, mm	10.9 (8.4, 14.6)	11.0 (8.0, 15.2)
Reference diameter, mm	3.45 (3.04, 3.82)	3.46 (2.97, 3.98)

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty; SVG, saphenous vein graft; and TIMI, Thrombolysis in Myocardial Infarction. Values are median (25th, 75th percentiles) or number (%) of patients in each category unless otherwise indicated.

*Number (%) of patients having at least one lesion in the given location.

common morphology (54.1% for DCA; 58.4% for PTCA). An irregular contour or thrombus often was present.

Procedure Performance

The initial success rates varied, depending on whether success was determined by the clinical center or the core angiographic laboratory (Table 5). Success was not different in the two groups when site assessment was considered (98.0% for DCA; 97.4% for PTCA). With blinded core laboratory assessment, the success rate was significantly higher for DCA at 89.2% versus 79.0% for PTCA. With QCA, the initial minimum luminal diameter was 0.92 mm for DCA and 1.03 mm for PTCA, and the corresponding diameter stenoses were 73.7% and 71.7% (Table 7). The initial gain achieved by treatment was significantly greater after DCA (1.45 versus 1.12 mm for PTCA, $P<.001$), so the postprocedure diameter stenosis was also less (31.5% versus 37.6% for PTCA, $P<.001$).

Predilatation was common in the DCA patients (Table 5). Other adjunctive devices were also used more frequently in these patients: 28.2% versus 14.1% of PTCA patients ($P=.003$). Patients undergoing DCA also required more radiographic contrast (225 versus 175 mL for DCA and PTCA, respectively) and had longer procedure times.

TABLE 4. Lesion Morphology

	DCA, n=146	PTCA, n=154
Eccentric	79 (54.1)	90 (58.4)
Irregular contour	72 (49.3)	81 (52.6)
Thrombus present	78 (53.4)	80 (52.0)
Ostial	29 (19.9)	27 (17.5)
Moderate angulation (≥45°)	14 (9.6)	11 (7.1)
Moderate tortuosity (2° to 60° or 1° to 90°)	8 (5.5)	9 (5.8)
Mild tortuosity (1° to 60°)	19 (13.0)	23 (14.9)

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty. Values are the number (%) of patients in each category.

Complications

The in-hospital rates for most major complications were similar in the two treatment groups (Table 6). Mortality was low (2.0% for DCA; 1.9% for PTCA), as was the need for coronary bypass graft surgery. The most important differences were in the rate of acute myocardial infarction and distal embolization. The incidence of Q-wave myocardial infarction was low in each group (1.3% for atherectomy; 1.9% for PTCA). There was a trend toward more non–Q-wave myocardial infarction after DCA (16.1%) than after PTCA (9.6%, $P=.09$). This usually happened in association with distal embolization, which occurred significantly more often with DCA ($P=.012$). However, abrupt closure of the treated segments was low in both treatment arms. With the composite adverse end point, there was a trend for a higher rate in the DCA group, mainly because of the excess non–Q-wave myocardial infarctions ($P=.059$) (Table 6).

Follow-up

The rate of angiographic follow-up for the entire cohort was 80% after a median of 5.9 months (Table 7). The primary end point of angiographic restenosis, >50% stenosis after an initially successful procedure, occurred less often with DCA (43.2% versus 52.1% using site readings and 45.6% versus 50.5% using QCA readings); however, the difference was not significant.

With continuous QCA data, the initial gain with atherectomy was greater: 1.45 versus 1.12 mm with PTCA. At follow-up, the late loss was also somewhat greater (0.62 versus 0.53 mm). At 6 months, the net gain with DCA was still greater (0.68 versus 0.50 mm), but this was not significant ($P=.066$) and the variability was high.

Figs 1 and 2 show the distribution of lesions. The initial minimum luminal diameter achieved with DCA was significantly larger. By the time of the follow-up angiogram, the minimum lumen diameter with DCA remained larger, but it was no longer significant. The distribution of follow-up stenoses showed that the most common follow-up diameter stenosis for directional coronary atherectomy was 30% to 40%, while with PTCA it was 40% to 50% (Fig 2). Again, this was not significantly different ($P=.10$).

Clinical follow-up data were available for 300 patients (98%) during a median follow-up of 6.2 months (Table 8). Six-month survival was 95.3% for DCA and 92.3% for PTCA ($P=.411$). Q-wave infarction was rare in both groups (2.7% for DCA; 4.0% for PTCA), as was the development of stroke. Survival without repeated coronary bypass graft surgery was also excellent: 94.5% and 95.3% for DCA and PTCA, respectively. The survival rate without repeated percutaneous target-vessel inter-

TABLE 5. Procedure Performance

	DCA, n=149	PTCA, n=156	P
Success (≤50% residual stenosis)			
Site assessment	144 (98.0)	151 (97.4)	
Core laboratory assessment	124 (89.2)	117 (79.0)	.019
Predilatation	23 (15.4)	....	
Maximal equipment size			
6F	19 (13.3)	<4.0 mm, 93 (62.8)	
≥7F	124 (86.7)	≥4.0 mm, 55 (37.2)	
Use of PTCA*	36 (24.2)	....	
Use of DCA	....	7 (4.5)	
Perfusion balloon	7 (4.7)	16 (10.3)	
Stent	0 (0.0)	2 (1.3)	
Laser	0 (0.0)	0 (0.0)	
Use of any of the above devices	42 (28.2)	22 (14.1)	.003
Dye, mL	225 (160, 300)	175 (130, 250)	
Fluoroscopy time, min	25 (17.1, 39.8)	17.0 (12.0, 24.8)	
Catheterization laboratory time, min	120 (91, 159)	99.5 (71, 130)	

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty. Values are median (25th, 75th percentiles) or the number (%) of patients in each category.
*Not predilatation.

vention was 86.8% for DCA patients versus 77.6% for PTCA patients (P=.041).

Discussion

This randomized trial of DCA versus PTCA documented that DCA resulted in a higher angiographic success rate and larger initial improvement in graft dimensions for de novo vein graft lesions. Given the large number of patients who have undergone coronary bypass graft surgery with venous conduits and the well-documented continuous rate of attrition in these grafts, treating these patients will continue to be a significant clinical problem.[23,23] The underlying pathophysiology in these patients is complex, with degenerated atheromatous lesions and often superimposed thrombus.[24-29] The results of dilatation depend in part on the age of the graft, the discrete (versus diffuse) nature of the lesion, and the location of the stenosis in the graft. Treatment of older grafts, >3 to 5 years old, and stenosis of the aortic origin or in the body of the graft have been associated with markedly increased restenosis rates.[2,5,9,10]

DCA has been used relatively frequently in venous conduits because of their lack of side branches, their usually straight and nontortuous course, and their large size. In the initial DVI Registry, 17% of cases involved treatment of vein grafts.[8] Restenosis rates in these and other series have varied, while embolization has been relatively low.[7,8,13-16,30]

Although both continuous and discrete dichotomous criteria were used to define restenosis, the latter was chosen as the primary end point using a definition of >50% diameter stenosis at follow-up. Restenosis defined in this manner occurred in a similar proportion of patients who received DCA (45.6%) or PTCA (50.5%, P=.491). This rate of restenosis after DCA is similar to that previously reported by Garratt et al,[13] who found a restenosis rate of 42% in patients treated for de novo vein graft lesions in whom there was no deep vessel wall resection. It is lower than other series have documented.[31] An equally important finding was that the restenosis rate in these 9.7-year-old vein grafts after PTCA was considerably lower (50%) than that previously recorded.[2,10] This contrasts with published series of

TABLE 6. Acute Complications

	DCA			PTCA			
	In Laboratory	In Hospital	Total	In Laboratory	In Hospital	Total	P
Death	0 (0)	3 (2.0)	3 (2.0)	0 (0.0)	3 (1.9)	3 (1.9)	1.000
CABG		1 (0.67)	1 (0.67)		2 (1.3)	2 (1.3)	1.000
Emergency CABG		1 (0.67)	1 (0.67)		1 (0.64)	1 (0.64)	1.000
Myocardial infarction	10 (6.7)	17 (11.4)	26 (17.4)	8 (5.1)	10 (6.4)	18 (11.5)	.142
Non-Q wave	10 (6.7)	15 (10.1)	24 (16.1)	6 (3.8)	9 (5.8)	15 (9.6)	.090
Q wave	0 (0)	2 (1.3)	2 (1.3)	2 (1.3)	1 (0.64)	3 (1.9)	1.0
Acute closure	5 (3.4)	2 (1.3)	7 (4.7)	4 (2.6)	0 (0.0)	4 (2.6)	.369
Distal embolization	20 (13.4)		20 (13.4)	8 (5.1)		8 (5.1)	.012
Perforation	1 (0.67)		1 (0.67)	0 (0.0)		0 (0.0)	.489
Stroke	0 (0.0)	2 (1.3)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	.238
Composite end point*			30 (20.1)			19 (12.2)	.059
No composite end points			119 (79.9)			137 (87.8)	

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass graft. Values are the number (%) of patients in each category.
*Composite of death, myocardial infarction, emergency bypass surgery, or acute closure.

TABLE 7. Quantitative Coronary Angiography Results

	DCA	PTCA	*P*
Restenosis (>50%)			
Site assessment	51 (43.2)	61 (52.1)	
Core laboratory assessment	47 (45.6)	48 (50.5)	.491
Preprocedure			
Reference size, mm	3.45 (3.04, 3.82)	3.46 (2.97, 3.96)	
MLD, mm	0.92 (0.70, 1.23)	1.03 (0.76, 1.29)	
Diameter stenosis, %	73.7 (65.6, 80.4)	71.7 (63.8, 79.2)	
Postprocedure			
Reference size, mm	3.44 (2.96, 3.83)	3.38 (2.99, 3.94)	
MLD, mm	2.49 (1.99, 2.95)	2.22 (1.83, 2.62)	
Diameter stenosis, %	31.5 (23.5, 39.4)	37.6 (28.6, 45.6)	<.001
6-Month follow-up			
Reference size, mm	3.42 (2.96, 3.88)	3.42 (2.98, 3.93)	
MLD, mm	1.78 (1.20, 2.27)	1.61 (0.92, 2.18)	
Diameter stenosis, %	47.3 (37.2, 67.9)	52.5 (40.2, 74.0)	.100
Acute gain, mm	1.45 (0.99, 1.92)	1.12 (0.78, 1.58)	<.001
Late loss, mm	0.62 (0.24, 1.40)	0.53 (0.10, 1.16)	.564
Net gain, mm	0.68 (0.20, 1.24)	0.50 (−0.09, 1.06)	.066
Loss index	0.40 (0.16, 0.84)	0.53 (0.10, 1.04)	.567

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty; and MLD, minimum luminal diameter. Values are median (25th, 75th percentiles) or the number (%) of patients in each category.

dilatation in old bypass graft stenoses, which document a restenosis rate of >60% to 70%. Platko et al[2] reported a restenosis rate of 83% in patients with vein grafts >3 years old, while Douglas et al[10] found a restenosis rate of 64% in patients with vein grafts >5 years of age. These previous studies did not have complete angiographic follow-up, however, so selection bias may explain the differences—more patients with symptomatic restenosis returned for follow-up angiography. Regardless of these considerations, PTCA still resulted in very reasonable intermediate-term outcomes in these patients.

Restenosis was also assessed with continuous QCA criteria. Although the initial gain with DCA was significantly greater, the loss was also somewhat greater. The overall net gain at the end of 6 months did remain larger with DCA (0.68 versus 0.50 mm), but not significantly so (P=.066). The relation between acute gain and late loss has been the subject of intense study.[17,18,32-34] A critical determinant of subsequent restenosis is the minimum luminal diameter achieved[17,32,33]; new devices may decrease angiographic restenosis by yielding significantly better initial results. The inevitable neointimal hyperplasia is then better tolerated and may not result in clinical restenosis. It is possible that the lack of decreased restenosis with DCA in this trial is related to the fact that a residual diameter stenosis of 31.5% remained.

Although the primary end point of this study was angiographic restenosis, important secondary end points were also assessed. As was true in CAVEAT-I[17] and CCAT,[18] DCA resulted in improved initial success rates and a larger median initial lumen. In DCA-treated patients in this series, the initial success rate was 89.2% versus 79.0% for PTCA patients, findings very similar to the success rates in CAVEAT-I. The median initial

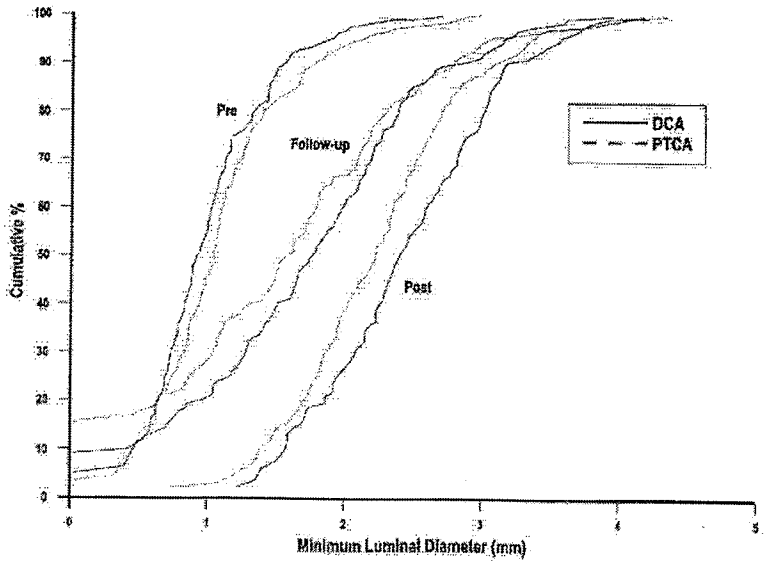

FIG 1. Graph showing preprocedure, postprocedure, and follow-up minimum luminal diameter by treatment group. DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty.

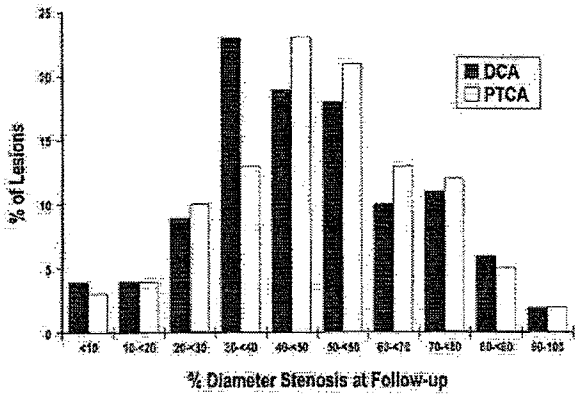

Fig 2. Bar graph showing distribution of follow-up stenoses by treatment group. DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty.

luminal gain was substantially larger: 1.45 mm for DCA versus 1.12 mm for PTCA. There were no differences in in-hospital mortality, need for coronary bypass graft surgery, and Q-wave myocardial infarction, but there was a trend toward increased non–Q-wave myocardial infarction in DCA patients and a significant increase in distal embolization ($P=.012$).

Follow-up Events

In CAVEAT-I, there was a moderate decrease in restenosis rates with DCA, but there was no difference in follow-up clinical events or need for repeated intervention.[17] In the CCAT trial, there were no differences with respect to repeated intervention.[18] In CAVEAT-II, although the 6-month cumulative mortality and Q-wave myocardial infarction rates were similar, there was a trend toward a decreased need for repeated target-vessel intervention or coronary artery bypass graft: 18.6% of DCA patients required repeated target-vessel revascularization versus 26.2% of PTCA patients. The need for any later intervention was also decreased in DCA patients, although the difference was smaller (24.8% versus 31.5% for DCA and PTCA, respectively). There are limited other well-controlled data on follow-up of patients treated for vein graft disease. It is known, however, that vein graft disease is progressive. Longer-term follow-up of these randomized patients in CAVEAT-II will be required to ascertain how long the modestly improved outcome with DCA lasts. It is also possible that this difference in favor of DCA could have resulted partly from the higher rate of distal embolization and non–Q-wave myocardial infarction in this group, leaving patients with a lower likelihood of undergoing symptom-driven repeated interventions.

TABLE 6. Six-Month Event-Free Survival Analysis

	Survival Rate		Log Rank
	DCA	PTCA	P
Death	0.953	0.923	.411
MI	0.798	0.837	.477
Q-wave MI (site)	0.973	0.960	.383
CABG	0.945	0.953	.952
Stroke	0.987	0.993	.972
Recatheterization	0.458	0.460	.500
Any intervention or CABG	0.752	0.685	.072
Any target intervention or CABG	0.814	0.738	.092
Any percutaneous intervention	0.805	0.723	.035
Any target percutaneous intervention	0.868	0.776	.041
Hospitalization	0.539	0.515	.862
Angina	0.583	0.604	.986
Canadian Heart Class angina >1	0.662	0.643	.794
Composite index*	0.597	0.557	.199

DCA indicates directional coronary atherectomy; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; and CABG, coronary artery bypass graft.
*Composite of death, myocardial infarction, bypass surgery, and repeat intervention.

Other interventional approaches are also being tested in patients with focal vein graft disease, particularly stents.[20,35-37] There is substantial enthusiasm because of the large initial minimum luminal diameter that can be achieved. The long-term results have not been subjected to a well-controlled trial, although one is now being planned. In a retrospective comparative assessment of a small group of patients, Pomerantz et al[20] found no difference in restenosis rates between DCA and one specific stent configuration.

Limitations

Some limitations should be kept in mind in the interpretation of this study. The first and perhaps most important is that the number of patients was relatively small. The estimated sample size was based on published rates of restenosis of de novo vein graft lesions treated with DCA and PTCA. While the restenosis rate for atherectomy was similar to what had been published, the PTCA restenosis rate was substantially better than expected for these 9.9-year-old grafts. Whether this better-than-expected outcome with PTCA related to patient selection, dilatation performance, or bias in the previous literature cannot be determined. If larger numbers of patients had been randomized, the differences between the two treatment arms might have been more striking. The second limitation relates to the fact that even in the group with the better postprocedure result (DCA), the diameter stenosis was 31.5%. More aggressive DCA or post-DCA dilatation might have resulted in better immediate postprocedure results and improved outcome, although this is controversial.

Conclusions

In this randomized trial, DCA resulted in a higher initial angiographic success rate and a larger initial improvement in graft dimensions than conventional PTCA with the use of QCA techniques. Achievement of this improved success rate was at least partially offset by the moderate initial increase in distal embolization and non–Q-wave myocardial infarction, which are probably the results of passage of the large atherectomy device and active debulking and manipulation of the lesion. There was a trend toward decreased performance of repeated target-vessel intervention at 6 months in patients treated with DCA, but there was no difference in angiographic restenosis rates. Overall, our findings suggest that both forms of revascularization are viable strategies for this complex patient group.

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Appendix

CAVEAT-II Sites and Investigators

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Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) Trial

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Background—Restenosis after percutaneous coronary intervention (PCI) is a major problem affecting 15% to 30% of patients after stent placement. No oral agent has shown a beneficial effect on restenosis or on associated major adverse cardiovascular events. In limited trials, the oral agent tranilast has been shown to decrease the frequency of angiographic restenosis after PCI.

Methods and Results—In this double-blind, randomized, placebo-controlled trial of tranilast (300 and 450 mg BID for 1 or 3 months), 11 484 patients were enrolled. Enrollment and drug were initiated within 4 hours after successful PCI of at least 1 vessel. The primary end point was the first occurrence of death, myocardial infarction, or ischemia-driven target vessel revascularization within 9 months and was 15.8% in the placebo group and 15.5% to 16.1% in the tranilast groups (P=0.77 to 0.81). Myocardial infarction was the only component of major adverse cardiovascular events to show some evidence of a reduction with tranilast (450 mg BID for 3 months): 1.1% versus 1.8% with placebo (P=0.061 for intent-to-treat population). The primary reason for not completing treatment was ≥1 hepatic laboratory test abnormality (11.4% versus 0.2% with placebo, P<0.01). In the angiographic substudy composed of 2018 patients, minimal lumen diameter (MLD) was measured by quantitative coronary angiography. At follow-up, MLD was 1.76±0.77 mm in the placebo group, which was not different from MLD in the tranilast groups (1.72 to 1.78±0.76 to 80 mm, P=0.49 to 0.89). In a subset of these patients (n=1107), intravascular ultrasound was performed at follow-up. Plaque volume was not different between the placebo and tranilast groups (39.3 versus 37.5 to 46.1 mm^3, respectively; P=0.16 to 0.72).

Conclusions—Tranilast does not improve the quantitative measures of restenosis (angiographic and intravascular ultrasound) or its clinical sequelae. (***Circulation.*** **2002;106:1243-1250.)**

Key Words: restenosis ■ revascularization ■ angiography ■ tranilast ■ percutaneous coronary intervention

Prevention of restenosis after percutaneous coronary intervention (PCI) remains a challenge despite stent deployment.[1–4] Although the frequency of restenosis has decreased to 15% to 30% with the widespread use of stent implantation, this still represents a large population of patients, many of whom will require a further revascularization procedure for restenosis. Systemic pharmacological approaches, in general, have been unsuccessful. Therefore, the results of 2 small placebo-controlled angiographic trials showing a statistically and clinically significant reduction in angiographic restenosis with tranilast[5,6] were seen as an opportunity to definitively assess this agent for the prevention of restenosis.

Tranilast inhibits the release or production of chemical mediators and cytokines by inflammatory cells and macrophages and interferes with the proliferation and migration of vascular medial smooth muscle cells induced by platelet-

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The Appendix is available in the online-only Data Supplement at http://www.circulationaha.org.

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TABLE 1. Patient Characteristics

Treatment Status and Patient Characteristics	Placebo (n=2298)	Tranilast BID for 1 mo		Tranilast BID for 3 mo	
		300 mg (n=2306)	450 mg (n=2280)	300 mg (n=2300)	450 mg (n=2300)
US/rest of world, %	43.8/56.2	43.8/56.2	43.9/56.1	43.8/56.2	43.7/56.3
Completed/withdrew treatment, %	85.3/14.7	79.0/21.0	75.6/24.4	76.5/23.5	68.9/31.1
Males	1777 (77.3)	1774 (76.9)	1771 (77.7)	1785 (77.6)	1786 (77.7)
Age, y	60.2±10.5	60.1±10.4	60.3±10.4	60.4±10.5	60.2±10.3
Diabetes	553 (24.1)	523 (22.7)	533 (23.4)	546 (23.7)	529 (23.0)
Hypertension	1429 (62.2)	1391 (60.3)	1350 (59.2)	1435 (62.4)	1408 (61.2)
Congestive heart failure	144 (6.3)	145 (6.3)	142 (6.2)	124 (5.4)	141 (6.1)
Statin use	1703 (74.1)	1702 (73.8)	1646 (72.2)	1680 (73.0)	1661 (72.2)
History of angioplasty	705 (30.7)	704 (30.5)	716 (31.4)	738 (32.1)	694 (30.2)
History of CABG	705 (30.7)	704 (30.5)	716 (31.4)	738 (32.1)	694 (30.2)
History of MI	890 (38.7)	904 (39.2)	873 (38.3)	911 (39.6)	875 (38.0)
Recent MI (index PCI reason)	293 (12.7)	305 (13.3)	302 (13.3)	282 (12.2)	300 (13.1)
Unstable angina	649 (28.2)	672 (29.1)	664 (29.1)	652 (28.4)	680 (29.6)
Multivessel disease	406 (17.7)	402 (17.4)	394 (17.3)	431 (18.7)	416 (18.1)
Restenotic vessel	349 (15.2)	385 (16.7)	355 (15.6)	372 (16.2)	362 (15.7)
In-stent restenosis	266 (11.6)	306 (13.3)	285 (12.5)	304 (13.2)	286 (12.4)
No. target vessels	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.4
No. target lesions	1.4±0.7	1.4±0.7	1.4±0.7	1.4±0.7	1.4±0.7
Target vessel site*					
Graft	107 (4.7)	92 (4.0)	119 (5.2)	104 (4.5)	103 (4.5)
LAD	902 (39.3)	900 (39.0)	863 (37.9)	892 (38.8)	932 (40.5)
Right coronary artery	1069 (32.3)	1124 (33.8)	1066 (32.6)	1093 (32.5)	1094 (32.4)
Circumflex	792 (23.9)	738 (22.2)	772 (23.6)	806 (24.0)	747 (22.1)
Left main	29 (0.9)	20 (0.6)	20 (0.6)	19 (0.6)	30 (0.9)
Angioplasty with stent(s)	1935 (84.2)	1920 (83.3)	1917 (84.1)	1921 (83.5)	1944 (84.5)
Lesion diameter <2 mm	548 (99.5)	536 (98.4)	527 (98.7)	554 (99.3)	550 (98.6)
Vessel length, mm					
>20	48 (8.7)	62 (11.4)	50 (9.4)	60 (10.8)	73 (13.1)
10–20	279 (50.6)	274 (50.3)	266 (49.8)	277 (49.6)	262 (47.0)
Vessel stenosis, %	84.1±12.0	84.4±12.0	84.3±11.8	84.0±12.4	83.8±12.5
Lesion morphology					
Type A	557 (17.3)	529 (16.3)	522 (16.4)	557 (17.0)	515 (15.8)
Type B1	977 (30.4)	1054 (32.4)	1014 (31.8)	1014 (30.9)	1011 (30.9)
Type B2	1194 (37.2)	1206 (37.1)	1149 (36.0)	1187 (36.2)	1220 (37.3)
Type C	477 (14.9)	452 (13.9)	496 (15.6)	513 (15.7)	514 (15.7)
Total occlusion	202 (6.3)	232 (7.1)	211 (6.6)	222 (6.8)	233 (7.1)
GPIIb/IIIa agents	855 (37.2)	831 (36.0)	827 (36.3)	830 (36.1)	850 (37.0)
Thienopyridines†	2061 (90)	2056 (89)	2053 (90)	2052 (89)	2069 (90)

Values are given as n (%) or mean±SD unless otherwise indicated. LAD indicates left anterior descending coronary artery; GP, glycoprotein.

*Not additive because some patients had >1 target vessel and "other" vessel sites.

†Only 22.8% to 24.5% of patients received ticlopidine; the remainder received clopidogrel.

derived growth factor and transforming growth factor-β_1.[7] The anti-inflammatory effects of tranilast have been demonstrated by the inhibition of prostaglandin E_2, thromboxane B_2, transforming growth factor-β_1, and interleukin-8 in in vitro models and by attenuation of the proinflammatory activity of human monocytes.[7] In addition, in various animal models, tranilast has been shown to reduce neointimal and adventitial thickening after vascular wall injury.[8,9]

In 2 angiographic trials, tranilast (600 mg a day for 3 months) decreased the proportion of nonstented patients with restenosis assessed by quantitative coronary angiography. Restenosis occurred in 60% of the patients treated with

TABLE 2. Results of Primary Composite End Point of MACE

Primary Efficacy End Point	Placebo (n=2298)	Tranilast BID for 1 mo 300 mg (n=2306)	Tranilast BID for 1 mo 450 mg (n=2280)	Tranilast BID for 3 mo 300 mg (n=2300)	Tranilast BID for 3 mo 450 mg (n=2300)
At least 1 MACE,* n (%)	358 (15.7)	352 (15.4)	351 (15.5)	363 (16.0)	364 (16.0)
Hazard ratio (95% CI)		0.98 (0.85–1.14)	0.98 (0.84–1.13)	1.02 (0.88–1.18)	1.02 (0.88–1.18)
P vs placebo†		0.81	0.77	0.81	0.77

*Risks are Kaplan-Meier product-limit estimates.
†Derived from log-rank test.

placebo compared with 17% of the patients treated with tranilast in one of the trials ($P<0.001$)[5] and in 47% of the patients treated with placebo compared with 23% of the patients treated with tranilast in the other trial ($P<0.001$).[6] In a concurrent controlled study, patients who were stented were compared with those who were treated with both tranilast and stent[10]; there was a reduction in angiographic restenosis from 45% to 26% ($P<0.05$).

These trials, although provocative, were limited in scope and not adequately powered to document statistical differences in clinical outcomes. Accordingly, the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial was designed to evaluate the effects of tranilast on major adverse cardiovascular events (MACEs) as well as quantitative angiographic and intravascular ultrasound (IVUS) end points.

Methods

Study Design

The PRESTO trial has been previously described and was a double-blind, placebo-controlled, parallel group study of patients after PCI.[11] Successful PCI was defined as at least 1 vessel stenosis improved to <50% residual stenosis without the occurrence of MACE before the first dose of study medication. The type of intervention performed was at investigator discretion, with the exclusion of experimental procedures, which included intracoronary radiation at the time of the trial. The protocol and informed consent were approved by a human research or ethics committee at each institution and the medical products agencies of the country when required. Patients were randomized to receive 1 of 5 treatments: placebo or tranilast at 300 or 450 mg BID for 1 or 3 months. An angiographic substudy (2000 participants) was also prespecified; in this substudy, consecutive patients enrolled at selected sites were required to undergo follow-up angiography at 9 months (or sooner if clinically warranted). Some of these sites also obtained follow-up intravascular ultrasound (IVUS) evaluations (for 1000 patients). When the enrollment in the substudies was complete, these sites then enrolled the patients into the general protocol. A battery of laboratory tests was performed weekly for 4 weeks and then every other week for 2 months. All blood samples were analyzed by central laboratories that used the same methodology. Sites were instructed to use the term "hepatic function abnormal" when the result of at least 1 hepatic laboratory test was >3 times the upper limit of normal (ULN) and either alkaline phosphatase or total bilirubin reached ULN. Increases in transaminase levels and hyperbilirubinemia were defined as being 3 times ULN, and indirect bilirubin was defined as twice ULN. Abnormal creatinine was defined as an increase of ≥50% to a level of at least 1.2 mg/dL or a serum creatinine level of >2 mg/dL on 2 consecutive occasions. Anemia was defined as a hemoglobin of <10 g/dL or a decrease from baseline of ≥2 g/dL.

The primary efficacy end point was the first occurrence of MACE within 9 months. Secondary end points were the components of MACE: all-cause mortality, myocardial infarction (MI), and ischemia-driven target vessel revascularization. To avoid the criticism of angiographic restenosis being ascribed to this end point, the investigators had to identify and document signs of ischemia before a repeat angiogram. MI was defined as having at least 2 of the following: (1) characteristic ischemic pain lasting ≥20 minutes, (2) creatine kinase >3 times ULN and creatine kinase-MB >2 times ULN, or (3) development of a new >40-ms Q waves in at least 2 adjacent ECG leads or new dominant R waves in V_1. Ischemia-driven revascularization was defined as intervention for chest pain or a positive test for ischemia (exercise stress test, stress echocardiogram, 24-hour Holter monitor, resting ECG evidence of ST-segment depression or elevation in >1 lead, or radionuclide study showing a reversible defect). An independent clinical event committee confirmed any MACE.[11] Other major secondary variables of interest included minimal lumen diameter (MLD) by quantitative coronary angiography and plaque volume by IVUS. As previously described,[11] the angiograms and IVUS films were read by 2 laboratories each. Both angiography laboratories used the Cardiovascular Measurement System (Medis Medical Imaging Systems) for quantitative measurements. Restenosis was defined as ≥50% stenosis in a treated segment at follow-up. To compare the restenosis rates for tranilast with those previously reported by Tamai and colleagues,[5,6] restenosis was also analyzed as ≥50% loss of acute gain.

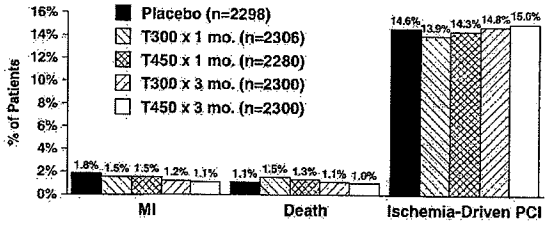
Power Calculations and Statistical Analysis

An expected incidence of 18% in the primary MACE end point based on prior published trials, including the results of the Evaluation of Platelet IIB/IIIA Inhibitor for STENTing (EPISTENT) trial,[12] was used for calculations of sample size. The overall type I error was selected so that the statistical evidence of efficacy would be equivalent to that provided by 2 positive trials at a level of significance of 0.05 and also to control for multiple group comparisons. Randomizing 2300 patients to each group provided 90% power to detect a reduction from 18% to 12.6% (30% relative reduction) among any or all tranilast groups by using 2-sided log-rank tests with an overall α value of 0.00125.[13,14]

An intent-to-treat population was analyzed for the primary analysis, which was defined as all randomized patients who received at least 1 dose of study medication. The frequency of the first occurrence of MACE was analyzed by using a modified Bonferroni procedure.[15] Significance levels for pairwise comparisons with placebo were derived from log-rank tests, stratifying for center. Cox proportional hazards models were used to calculate hazard ratios (tranilast/placebo) with associated 95% CIs. In the model, the independent variables were center and treatment. Kaplan-Meier curves were calculated for MACE as well.

In the angiographic substudy, the minimum clinically relevant treatment difference was assumed to be 0.2 mm (±SD of 0.7 mm) between treatment groups at follow-up.[4] Therefore, 400 patients per arm were required to detect this reduction with 93% power at an α value of 0.05. To ensure that 2000 patients had follow-up angiograms, the protocol required that 2666 patients be enrolled in this substudy. Dichotomous restenosis rates were also analyzed.

In the IVUS substudy, the minimum treatment difference considered clinically relevant was assumed to be a 20% difference between treatment groups at follow-up. Based on a normal distribution curve in ≈100 patients at the Stanford Core Laboratory, the mean plaque



KEY: T300 x 1 mo. = tranilast, 300 mg bid for one month; T450 x 1 mo. = tranilast, 450 mg bid for one month; T300 x 3 mo. = tranilast, 300 mg bid for three months and T450 x 3 mo. = tranilast, 450 mg bid for three months.

Note: % of patients is higher than first occurrence of MACE because all events of the components of MACE are counted.

Figure 1. Percentage of patients with each component of MACE.

volume was expected to be 41.91 mm^3 (±SD of 17.67 mm^3). With this assumption, 140 stented patients per group were required to detect a 20% reduction with 80% power at an α value of 0.05.

Results

Patient Characteristics

Four hundred thirty-two centers (224 in the United States, 166 in Western Europe, 27 in Canada, 7 in Eastern Europe, and 8 in Australia/South Africa) enrolled 11 484 patients between April 1999 and July 2000, with the last patient visit on April 18, 2001. The groups were well matched and consistent with the expected moderate risk of restenosis based on the proportion of patients with factors known to be associated with restenosis (Table 1). The mean number of target vessels was 1.2, and the mean number of target lesions was 1.4.

The angiographic subset (n=2018) was not clinically different from the population as a whole or from a random sample of patients not in the angiographic subset: 77% were male, 40% had a previous MI, 24% were diabetic, and 13% underwent PCI after an MI. The mean numbers of target vessels and lesions were identical to those of the general population: 15% had restenotic lesions, 12% had in-stent restenosis, and 83% received a stent. The IVUS population (n=1107) was similar to the PRESTO population and similar to a random sample of patients not in the angiography subset (data not shown). However, there was some evidence that the patients in the IVUS subset had larger vessel diameters (mean stent diameter of 3.4 versus 3.2 mm for the angiographic subset). A total of 1180 lesions were evaluated by IVUS; only 73 (6%) were in nonstented vessels.

MACE During 9 Months

The frequency of the first occurrence of MACE in the placebo group was slightly lower than predicted (15.7%). The MACE rate was virtually identical among all 4 tranilast groups, and there was no decrease from placebo (Table 2). MACE rates were driven by ischemia-induced target vessel revascularization; the frequency of death and MIs were low, occurring in only 1% to 1.8% of the population (Figure 1). Extensive subgroup analyses were performed. The relative risk of MACE by subgroups (Figures 2 and 3) revealed no differences between tranilast and placebo in any subgroup. As expected, mortality was low in this study population. No

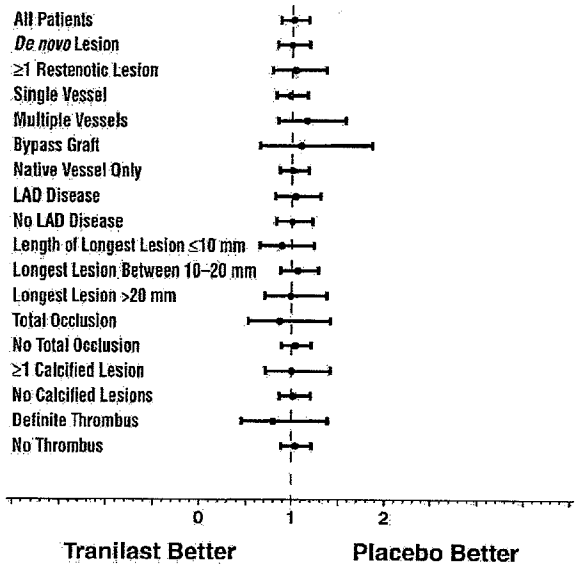


Figure 2. Subgroup analyses of MACE outcome differences between placebo and tranilast.

trends in favor of any dose of tranilast were observed for death or ischemia-driven target vessel revascularization. To test whether early withdrawals were responsible for the lack of effect, an analysis was performed in patients who completed treatment with no treatment effect observed.

A possible trend in favor of tranilast (450 mg BID) compared with placebo was observed in the frequency of follow-up MIs (hazard ratio 0.62, 95% CI 0.38 to 1.03; $P=0.061$). To ascertain the strength of this trend, an analysis of patients who completed at least 84 days of treatment was undertaken; the hazard (tranilast/placebo) ratio for follow-up

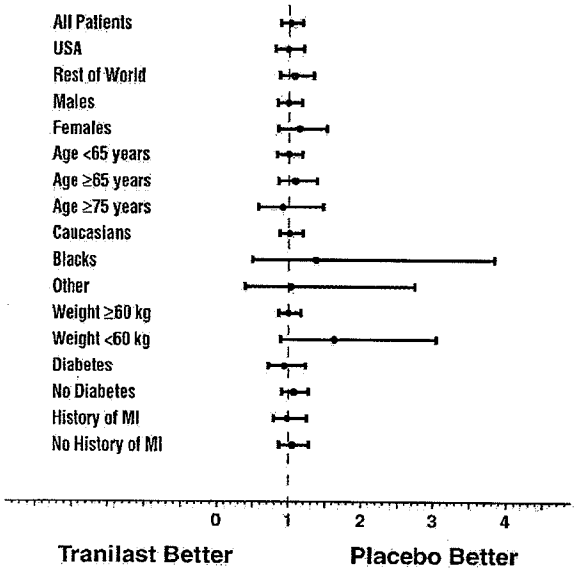


Figure 3. Subgroup analyses of MACE outcome differences between placebo and tranilast.

TABLE 3. Quantitative Angiographic Analysis

Angiographic End Points by Patient	Placebo (n=420)	Tranilast BID for 1 mo 300 mg (n=407)	Tranilast BID for 1 mo 450 mg (n=389)	Tranilast BID for 3 mo 300 mg (n=415)	Tranilast BID for 3 mo 450 mg (n=387)
Baseline					
Reference diameter, mm	2.90±0.51	2.92±0.54	2.94±0.52	2.93±0.51	2.92±0.57
MLD, mm	0.81±0.43	0.86±0.48	0.79±0.47	0.85±0.45	0.83±0.42
Stenosis, %	72.1±14.2	71.1±14.6	73.0±14.9	70.8±14.9	71.6±13.2
MLD immediately after PCI, mm	2.70±0.56	2.69±0.60	2.72±0.58	2.74±0.56	2.74±0.62
Acute gain in MLD, mm	1.89±0.64	1.83±0.63	1.94±0.67	1.89±0.65	1.91±0.64
Residual stenosis, %	10.0±11.9	10.5±13.1	9.5±12.4	9.3±12.4	9.7±11.6
MLD at follow-up,* mm	1.76±0.77	1.72±0.80	1.77±0.76	1.75±0.79	1.78±0.77
Change in MLD from immediately after PCI (late loss), mm	0.96±0.76	0.972±0.75	0.972±0.79	1.00±0.79	0.97±0.76
% Stenosis at follow-up	39.5±23.8	40.5±24.0	38.8±23.1	39.7±23.4	38.7±22.9
Ratio of late loss/acute gain	0.52±0.45	0.57±0.50	0.49±0.48	0.54±0.44	0.52±0.41
Restenosis rate: ≥50% stenosis					
Lesions, %	30.1	29.8	28.5	29.8	29.0
Patients,† %	33.3	35.1	33.4	35.2	32.3

Values are mean±SD unless specified otherwise.
*In patients with multiple lesions/vessels, MLD was averaged.
†Restenosis of any lesion.

MI decreased to 0.44 (95% CI 0.23 to 0.85), and the significance was $P=0.012$.

Angiographic and IVUS Results

Informed consent was given by 2682 patients for the angiographic substudy, and follow-up was terminated when 2018 patient follow-up films had been submitted to the core laboratories (75%). At the time of the index procedure, the mean target vessel reference diameters and MLD as well as the percent stenosis and residual stenosis were similar across treatment groups. There were no statistically or clinically significant differences in the angiographic variables immediately after the index PCI or at follow-up (Table 3). These data are represented in Figure 4 by the cumulative curves of MLD in the placebo group and the highest dose/duration of the tranilast group.

Angiographic restenosis by patient and lesion (Table 3) showed no significant differences between tranilast and placebo ($P=0.46$ to 1.00). However, there was a significant ($P<0.001$) correlation between the frequency of restenosis across treatment groups and the occurrence of MACE (Table 4). This was again related to target vessel revascularization. Patients who had no evidence of restenosis with ≥50% stenoses by angiography were significantly less likely to have a MACE.

There were no clinically or statistically significant differences among the treatment groups in any of the intracoronary ultrasound measurements (Table 5).

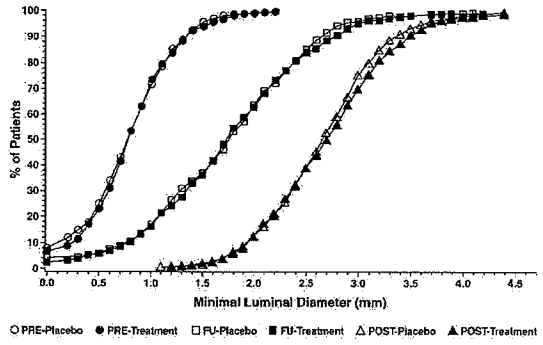


Figure 4. Cumulative distribution curves of MLD for highest dose/duration of tranilast (450 mg BID for 3-month group) compared with placebo.

Adverse Events

The most frequently reported adverse experiences were laboratory test abnormalities consisting of hyperbilirubinemia, elevations in hepatic (transaminase) enzymes, and hepatic function abnormal (Table 6). In addition, there were increases in serum creatinine and decreases in hemoglobin reported as anemia. The majority of the increases in serum creatinine

TABLE 4. Correction Between Angiographic Restenosis and MACE

Association With Restenosis	Angiographic Restenosis ≥50% Stenosis Yes, n (%)	≥50% Stenosis No, n (%)	Total, n (%)
MACE			
Yes	313 (46)*	73 (5)	386 (19)
No	371 (54)	1261 (95)*	1632 (81)
Totals	684 (100)	1334 (100)	2018 (100)

*Positive predictive value=313/684=0.458 (±0.019); negative predictive value=1261/1334=0.945 (±0.006); P value from χ^2 test for association ($P<0.001$).

TABLE 5. IVUS Analysis at Follow-Up of Patients Who Had at Least 1 Stented Vessel

IVUS End Points at Follow-Up	Placebo (n=224)	Tranilast BID for 1 mo 300 mg (n=211)	Tranilast BID for 1 mo 450 mg (n=222)	Tranilast BID for 3 mo 300 mg (n=230)	Tranilast BID for 3 mo 450 mg (n=220)
Plaque volume, mm^3					
Mean±SD	39.3±26.2	37.5±26.9	45.3±32.3	45.5±47.1	46.1±36.7
P vs placebo	...	0.72	0.22	0.20	0.16
Mean luminal area, mm^2					
Mean±SD	5.5±1.94	5.9±2.27	5.2±2.19	5.7±2.45	5.5±2.63
P vs placebo	...	0.19	0.42	0.42	0.93
Plaque area, mm^2					
Mean±SD	2.7±2.61	2.4±2.45	2.7±2.13	2.3±1.56	2.7±2.23
P vs placebo	...	0.32	0.93	0.16	0.97
Mean total vessel area, mm^2					
Mean±SD	5.7±3.0	6.9±3.0	7.4±3.2	6.2±3.5	4.8±2.8
P vs placebo	...	0.33	0.17	0.71	0.50

were 50% increases to values >1.2 mg/dL. Less than 1% of the patients in all treatment groups had a serum creatinine ≥2 mg/dL at the termination of double-blind treatment. The hepatic and renal laboratory abnormalities as well as anemia were related to both the dose of tranilast and the duration of tranilast treatment (ie, the higher the dose and the longer the duration of treatment, the higher was the frequency). These laboratory abnormalities, when followed, were all reversible with discontinuation of the study medication.

Discussion

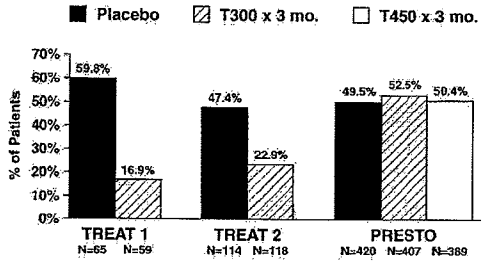
Tranilast was not significantly more effective than placebo at total daily doses of 600 and 900 mg a day administered for 1 or 3 months in reducing the frequency of MACE or angiographic restenosis in a broad group of patients undergoing PCI. In addition, it did not decrease neointimal hyperplasia as measured by IVUS. The incidence of MACE in the placebo group was 15.7%, and the incidence of MACE in the tranilast groups ranged from 15.5% to 15.0%. In the angiographic

TABLE 6. Most Frequently (≥2%) Reported Adverse Experiences Considered at Least Possibly Related to Tranilast

WHO Body System and Preferred Term	Placebo	Tranilast BID for 1 mo 300 mg	Tranilast BID for 1 mo 450 mg	Tranilast BID for 3 mo 300 mg	Tranilast BID for 3 mo 450 mg
Gastrointestinal					
Abdominal pain, %	<1	<1	1	2	2
Nausea, %	1	1	2	1	2
Liver/biliary system					
Hyperbilirubinemia, %	<1	2	8	4	12
Hepatic function abnormal, %	<1	5	7	7	9
Hepatic enzymes increased, %	<1	3	4	5	6
SGPT increased, %	1	2	3	3	3
Metabolic					
Creatinine increased, %	1	2	3	3	5
Red blood cells					
Anemia, %	<1	<1	2	1	4
Skin and appendages					
Rash, %	1	<1	<1	1	2
Urinary system					
Dysuria, %	<1	2	2	2	3

WHO indicates World Health Organization; SGPT, serum glutamic pyruvic transaminase. Events within body system are not additive because some patients are counted in multiple preferred terms listed under body system.

*Procedural injury includes hematoma, pain, oozing, pseudoaneurysm, and bruising at catheter insertion sight.



KEY: T300 x 3 mo. = tranilast, 300 mg bid for three months and T450 x 3 mo. = tranilast, 450 mg bid for three months.

Figure 5. Restenosis defined as ≥50% loss of acute gain in PRESTO vs TREAT 1 and TREAT 2 trials.

substudy, a ≥50% loss of acute gain was found in 50% of the patients treated with placebo and in 49% to 52% of the patients treated with tranilast. These findings are in contrast to the statistically significant and clinically relevant restenosis rates associated with tranilast treatment observed previously in the Tranilast Restenosis Following Angioplasty Trial (TREAT trial) (Figure 5).[5,6] In the TREAT 1 trial,[5] MLD at follow-up was 1.54 mm in the placebo group and 1.82 mm in the tranilast (600 mg) group (P=0.001). The MLD in the PRESTO trial at follow-up in the tranilast group was 1.76 mm, which was not different from that observed with tranilast (600 mg for 3 months) in the TREAT trial. What is different is that the MLD in the placebo group in the PRESTO trial was larger (at 1.75 mm). Immediately after PCI, the MLD in the TREAT 1 trial was significantly larger in the tranilast group than in the placebo group (2.27 versus 1.54 mm, respectively; P=0.029). MLD was not reported for the TREAT 2 trial.[6]

In the TREAT trials, restenosis defined as a ≥50% loss of acute gain was reported for 17% and 23% (Figure 5) of the patients. TREAT 1 reported that 43.1% of the placebo-treated patients had a ≥50% stenosis compared with 20.3% of the patients treated with tranilast (600 mg a day). Compared with the PRESTO trial, these trials were small and generally included patients at lower risk of restenosis. In the TREAT 1 trial, 85 or 86 patients per treatment group were randomized, and in the second TREAT trial, 114 to 118 were randomized. These trials excluded lesions in the side branches, left main disease, grafts, lesions >20 mm, lesions responsible for MIs within 2 weeks of study entry, patients with no thrombus or dissection, and Thrombolysis in Myocardial Infarction (TIMI) grades >1. All of these exclusion criteria were allowed in the PRESTO trial. In the TREAT trials, patients who did not complete treatment were eliminated from analysis; ≈28% of the patients were excluded. The PRESTO analysis was an intent-to-treat whereby all patients who received at least 1 dose of medication were included.

Two trials reported the frequency of MACE during a 1-year follow-up. In the TREAT 1 study,[5] there were no MIs or deaths. In the second, a concurrent control study in patients who underwent directional coronary atherectomy (DCA),[16] the frequency of MI was 0.7% in the DCA-only group compared with 0% in the DCA plus tranilast (600 mg a day for 3 months) group. These frequencies are based on a denominator of patients who completed the 3 months of treatment and were valid for efficacy analyses. To make like comparisons, the frequency of MI in the placebo group for those patients who completed 84 days in the PRESTO trial was calculated, and among those patients, a significant reduction in the frequency of MI was seen in the 3-month tranilast (450 mg BID) group compared with the placebo group (0.4% versus 1.6%, respectively; P=0.002). The beneficial effect of tranilast on the frequency of MIs may, in part, be due to its attenuation of the proinflammatory activity of human monocytes/macrophages.[7] Alternately, the reduction in the frequency of MIs may be the result of multiple analyses on multiple end points and, therefore, may be spurious.

Although there were no differences between the tranilast and placebo groups in the primary efficacy end point of MACE and in the secondary efficacy end point of angiographic restenosis, there were both dose-related and duration-related laboratory test abnormalities reported as adverse experiences. These abnormalities were reversible on the cessation of tranilast treatment. The adverse experience profile in the present study was similar to that reported by Tamai and colleagues.[5,6] Had the study met the primary efficacy criteria, it was believed that the benefit of reducing the incidence of MACE would outweigh the risk. However, even if the benefit observed in the reducing subsequent MIs proved to be reproducible, this advantage would probably still not outweigh the risk of developing liver laboratory test abnormalities.

The lack of efficacy demonstrated by tranilast in the PRESTO study was unexpected and clearly failed to confirm earlier reports.[5,6,10,16] This underscores and emphasizes the critical importance of subjecting the findings of studies limited in scope and sample size (even when "statistically significant") to robust, large-scale, definitive trials adequately powered to avoid type I errors.

Prevention of restenosis has been very difficult but remains very important because of recurrent symptoms and the need for subsequent procedures when restenosis occurs. Multiple device and medication strategies have been tested; typically, small experimental or pilot human studies form the rationale for larger more definitive studies. These larger definitive studies are aimed at overcoming the limitations of small studies. The PRESTO trial followed the same time course of other investigations, from small pilot studies to a definitive large study, which in this case was negative. Ever since the design and performance of the PRESTO trial, new data have accumulated that appear encouraging. Information continues to accumulate on the efficacy of vascular brachytherapy for treatment of in-stent restenosis (although not for prevention of initial restenosis). Even more exciting are the initial data on drug-coated stents, which dramatically prevent restenosis.

In conclusion, in this multicenter, large, randomized clinical trial, administration of tranilast in 2 different doses for 2 different durations was associated with no improvement in either angiographic or clinical restenosis compared with administration of placebo alone.

Appendix

Institutions and Investigators

Institutions and investigators who enrolled at least 45 patients in the PRESTO trial can be found in the online version of the present study, available at http://circ.ahajournals.org.

Core Laboratories

The authors wish to acknowledge the assistance in reading angiograms and IVUS films, which is contained in the online version of the present study.

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Final results of the CAPAS trial

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Background The Cutting Balloon (Interventional Technologies Inc) is a new-concept balloon that incorporates 3 to 4 blades to create sharp incisions on the luminal surface of the lesion during dilation without causing severe tearing injury to the vessel wall. It may reduce restenosis and improve clinical outcome.

Methods Two hundred forty-eight lesions were randomly assigned to Cutting Balloon angioplasty (CBA, 120 lesions) or conventional balloon angioplasty (PTCA, 128 lesions). Inclusion criteria were type B/C lesions (American College of Cardiology/American Heart Association classification) and reference diameter <3.0 mm by visual image on angiogram. Quantitative coronary angiography was performed before and after percutaneous coronary angioplasty and at 3-month follow-up. The primary end point was restenosis, defined as ≥50% diameter stenosis at follow-up. Clinical event rates at 1 year were assessed.

Results Baseline characteristics were similar. Reference diameter was small in both groups (2.16 vs 2.18 mm, CBA vs PTCA). Preprocedural percent diameter stenosis (%DS) was similar (69.8% vs 69.6%). However, postprocedural and follow-up %DS were lower (26.2% vs 28.9%, $P = .072$; 40.8% vs 47.5%, $P = .011$) in the CBA group. Restenosis was significantly lower (25.2% vs 41.5%, $P = .009$) in the CBA group. At 1 year, event-free survival was achieved in 72.8% of the CBA group and in 61.0% of the PTCA group ($P = .047$).

Conclusion These findings suggest that CBA provides superior angiographic and clinical outcomes in comparison with PTCA in small coronary arteries. (Am Heart J 2001;142:782-9.)

Restenosis remains the major limitation of the long-term benefit of coronary angioplasty.[1] Compared with conventional balloon angioplasty (PTCA), stents have significantly reduced the incidence of restenosis,[2,3] but these results were obtained in selected patients with relatively large vessels (diameter ≥3.0 mm) and simple lesions. The extension of stent indications to complex lesions and small vessels produces less favorable results.[4-13] In one recent study, stent restenosis results were reported to be as high as 56% for tubular stents in vessels ≤2.7 mm in diameter.[14] The reason for higher stent restenosis rates in small vessels appears to be due to the greater late lumen loss. Akiyama et al[15] reported that the loss index in small-vessel stenting is significantly higher than in large-vessel stenting (0.56 vs 0.45). PTCA continues to be commonly performed for such lesions. Recently, the Food and Drug Administration has approved a new balloon angioplasty device, Cutting Balloon (Interventional Technologies Inc), for treatment of highly resistant lesions. The Cutting Balloon has also been shown to be effective in reducing complex dissection rates as well as restenosis rates in small vessels.[16] In our study, we evaluated the effectiveness of the Cutting Balloon compared with the conventional balloon in patients with small-vessel coronary artery disease.

The Cutting Balloon is a device with 3 or 4 microtome sharp metal blades (0.25 mm high) mounted longitudinally on the surface of the balloon.[17] During dilation, the device produces 3 or 4 endovascular surgical incisions. An intravascular ultrasonographic study demonstrated that the longitudinal incisions in the plaque and vessel wall reduce true dissection rates as well as a nominal vessel area decrease.[18] Thus Cutting Balloon angioplasty (CBA) may limit the degree of traumatic vessel wall injury typically encountered in PTCA. Considering these data, we hypothesized that this device may reduce restenosis and improve the clinical outcome in small vessels.

Methods

Patients and study design

CAPAS (Cutting balloon Angioplasty vs Plain old balloon Angioplasty randomized Study in type B/C lesions) was a prospective, randomized, single-center study comparing CBA with PTCA in small coronary arteries. The angiographic inclusion criteria were (1) target vessel diameter of <3.00 mm by visual image on the angiogram and (2) lesion morphologic features of type B or C by the American College of Cardiology (ACC)/American Heart Association (AHA) classification. Heav-

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ily calcified lesions, angulated lesions (difficult to cross), unprotected left main lesions, bypass graft lesions, and culprit lesions for acute myocardial infarction (MI) within the previous month were excluded. Informed consent was obtained under a protocol approved by the institutional review board. Patients were randomized to CBA or PTCA. The primary end point was 90-day angiographic evidence of stenosis, defined as diameter stenosis of at least 50%. The secondary end point was event-free survival at 1 year.

Procedure

After standard preparation and local anesthesia, an 8F sheath was placed into the femoral or brachial artery, and a standard 8F guiding catheter was advanced through it. Intracoronary nitroglycerin (200 to 300 μg) was administered, followed by cine angiography of the culprit lesion in 2 orthogonal views. During coronary intervention, patients received an initial intravenous bolus of heparin (body weight, kg × 150 U) and were supplemented as needed to maintain an activated clotting time >300 seconds. By visual assessment, balloon size was determined and dilated with either conventional balloon or Cutting Balloon according to the randomization. CBA was performed with a maximum inflation pressure of 8 atm. The balloon inflation pressure for PTCA was not limited. In cases of suboptimal results, adjunctive high-pressure ballooning was performed by use of an identically sized conventional balloon in the CBA group. Stents were used as a bailout device if occlusive dissections could not be managed with prolonged inflation performed with autoperfusion balloons. Procedural success was defined as ≥20% reduction in stenosis and immediate postprocedural diameter stenosis <50%. After the procedure, synthetic platelet-aggregation inhibitors (aspirin 250 mg/dL or ticlopidine 200 mg/dL or cilostazol 200 mg/dL) were continued for at least 3 months.

Follow-up

In-hospital assessment was performed for all clinical outcomes including hemorrhagic and vascular complications and routine ascertainment of creatine kinase (CK) and CK-myocardial band (MB) before treatment and at 4 to 6 hours and 24 hours after the procedure. After patient discharge, clinical follow-up examinations were conducted on an outpatient basis at least once a month. Clinical follow-up was obtained at 3, 6, and 12 months for the occurrence of an adverse cardiac event (death, MI, or any repeat revascularization procedure). Angiography based on clinical indications before 3 months was allowed. However, if restenosis was not found, a subsequent angiogram was obtained after 3 months.

Angiographic analysis

All preprocedure, postprocedure, and follow-up angiography was conducted immediately after the administration of 200 μg of intracoronary nitroglycerin. Follow-up angiography was performed with guiding catheters at least 6F. Angiography was performed so that each lesion could be viewed from at least 2 angles. Off-line quantitative coronary angiography (QCA) was conducted. Calculations were performed with the Cardiovascular Measurement System (CMS-MEDIS Medical Imaging Systems) by an operator who was only provided with the edited cine films of before and after pictures to blind from the patient's group assignments. Lesion length, reference diameter (RD), minimal lumen diameter (MLD), and diameter stenosis (DS) were calculated. Acute gain was defined as the difference between pre-MLD and post-MLD. Late loss was defined as the difference between post-MLD and follow-up MLD. Loss index was calculated as late loss divided by acute gain. Angiographic restenosis was defined as a DS of >50%.

End points

The primary end point was 90-day angiographic evidence of stenosis defined as at least 50% of DS on the follow-up angiogram. The secondary end point was a composite end point, defined as whichever of the following occurred first: death, MI, coronary artery bypass surgery (CABG), or the need for repeat angioplasty within 3 months of the initial revascularization. Angiographic evidence of procedural success was defined as a reduction in stenosis to ≤50% by QCA. Clinical evidence of procedural success was defined as angiographic evidence of success without a major complication (death, MI, or CABG) during hospitalization. MI was defined as presence of new Q waves of at least 0.04 seconds' duration or a CK level or MB fraction at least twice the upper limit of normal. Revascularization of the target lesion was defined as angioplasty or CABG performed because of restenosis of the target lesion associated with recurrent angina or evidence of myocardial ischemia.

Statistical analysis

All analyses were conducted by the intention-to-treat method. Continuous variables were expressed as mean value ± SD. Variable categories were expressed as frequencies. The Student *t* test and nonparametric analysis by the Mann-Whitney *U* test were used for numerical comparisons between groups. The χ^2 test and the Fisher exact test were used for comparison of variable categories expressed as frequencies. Statview version 4.11 (Abacus Concepts) was used for data analysis. The Kaplan-Meier method was used to generate survival and event-free curves. Probability values of $<.05$ were considered significant. The current study, with a sample of 220 lesions evenly divided between 2 groups, had a power of 80% and a significance of 95% for detecting the reduction of the restenosis rate from 40% to 25%. To compensate for procedural failure and losses to follow-up, the sample was enlarged by 10%.

Results

Characteristics of the patients

From November 1995 to October 1997, 232 patients (248 lesions) were enrolled in the study. One hundred twenty lesions were assigned to CBA and 128 lesions to PTCA. Baseline clinical characteristics are shown in Table I. Baseline angiographic characteristics are shown in Table II. There were no differences in baseline characteristics between the 2 groups.

Procedural and early clinical outcome

Procedural and early clinical outcomes are shown in Table III. Of the 120 lesions randomized to the CBA

Table I. Baseline clinical characteristics

	CBA group (n = 114)	PTCA group (n = 118)
Age (y)	64 ± 8	65 ± 9
Male (%)	83	79
Diabetes mellitus (%)	38	32
Hypertension (%)	50	53
Hyperlipidemia (%)	53	53
Smoking (past or current) (%)	47	48
Prior MI (%)	39	39
Prior CABG (%)	6	7
Prior percutaneous coronary angioplasty (%)	25	22
No. of vessels diseased (%)		
1	48	50
2	39	37
3	13	13

Table II. Baseline lesion characteristics

	CBA group (n = 120)	PTCA group (n = 128)
Vessel treated (%)		
Left anterior descending artery	30	24
Right coronary artery	30	38
Left circumflex artery	40	38
Calcification (%)	41	46
Eccentric (%)	76	78
Bifurcated (%)	21	22
Angle ≥45 degrees (%)	9	19
Length >15 mm (%)	23	30
Lesion type (%)*		
B1	38	32
B2	37	48
C	25	20

*ACC/AHA classification.

Table III. Procedural variables

	CBA group (n = 120)	PTCA group (n = 128)	P value
Residual stenosis >50% (%)	1.7	3.9	.287
Stent implantation (%)	5.8	8.6	.402
Adjunctive directional coronary atherectomy (%)	0.8	0	.300
Delivery failure and crossover to PTCA (%)	6.7	0	.003
Final balloon size (mm)	2.64 ± 0.42	2.61 ± 0.35	.665
Balloon-artery ratio	1.25 ± 0.24	1.22 ± 0.19	.187
Maximum inflation pressure (atm)	6.4 ± 1.4	8.8 ± 2.7	<.0001
No. of inflations	2.5 ± 1.5	3.4 ± 3.3	.023
Follow-up term (d)	115 ± 38	112 ± 46	.595

group, 2 lesions had incomplete dilation (residual stenosis ≥50%) and underwent medical treatment. There were 8 delivery failures that were crossed over to PTCA. Seven lesions received stents for flow-limiting dissections and 1 lesion underwent directional coronary atherectomy for a flow-limiting flap. In 13 lesions, adjunctive high-pressure balloon was performed with use of an identically sized balloon because of suboptimal results. Of the 128 lesions randomized to the PTCA group, 5 lesions had incomplete dilation and underwent medical treatment. There were no delivery failures. Eleven lesions received stents for flow-limiting dissections. No perforations were observed in either group. Finally, it is worth noting that glycoprotein IIb3 inhibitors were not used in our study because of their unavailability in Japan.

According to the QCA, procedural success was obtained in 118 of the 120 lesions in CBA (98.3%) and in 123 of the 128 lesions (96.1%) in PTCA. The balloon/artery ratio (1.25 ± 0.24 vs 1.22 ± 0.19) was similar in both groups. The average maximum balloon pressure and the average number of inflations were smaller in the CBA group than in the PTCA group (6.4 ± 1.9 atm vs 8.8 ± 2.7 atm, $P < .0001$; 2.5 ± 1.5 vs 3.4 ± 3.3 inflations, $P = .023$). Lesions treated with other devices were excluded from this analysis.

Angiographic follow-up

Angiography was repeated at 3 months in 229 of the 241 lesions (95.0%) eligible for follow-up, 111 of 118 lesions (94.1%) in the CBA group and 118 of 123 lesions (95.9%) in the PTCA group. Table IV shows the angiographic results. At baseline, there was no difference in the reference diameter or the severity of stenosis between the 2 groups. After the procedure, residual DS in the CBA group tended to be lower than that in the PTCA group (26.2% ± 11.7% vs 28.9% ± 10.3%, $P = .072$) although fewer inflations and lower inflation pressures were used in the CBA group. At follow-up, residual DS in the CBA group was 14% lower in comparison with that in the PTCA group (40.8% ± 19.2% vs 47.5% ± 20.4%, $P = .011$). The cumulative distributions of the MLD and %DS are shown in Figures 1 and 2. The incidence of restenosis in the CBA group was 39% lower than in the PTCA group (25.2% vs 41.5%, $P = .009$). A subgroup analysis is shown in Table IV and Figure 3. Lesions were divided into 2 groups on the basis of the angiographic reference diameter before the procedure: group 1 included 130 lesions with a reference diameter <2.25 mm and group 2 included 99 lesions with a reference diameter ≥2.25 mm. In group 1, the incidence of restenosis in the CBA group was significantly lower compared with that in the PTCA group (24.2% vs 49.2%, $P = .003$). In group 2, there were no significant differences between the 2 groups (26.7% vs 33.3%, $P = .472$). Compared by the lesion morphologic features (ACC/AHA classification), the

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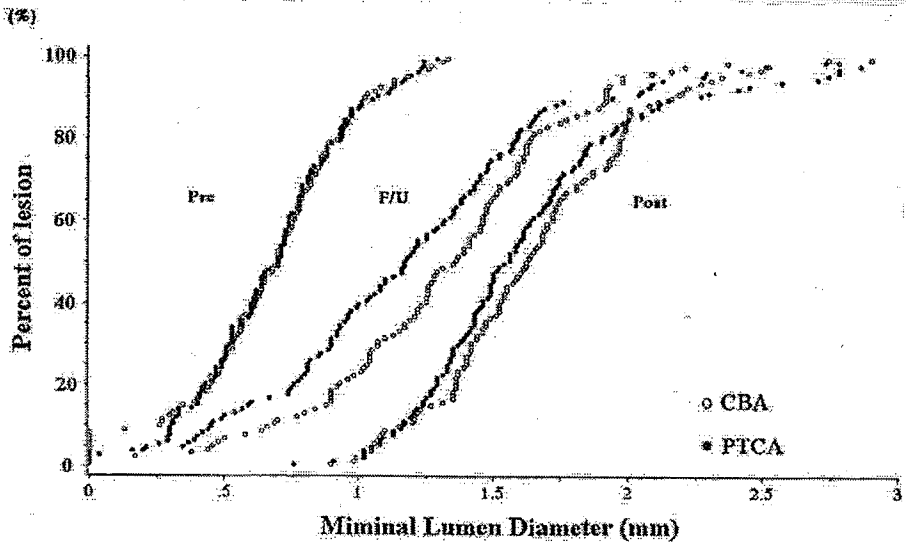
Figure 1



Cumulative distribution, MLD.

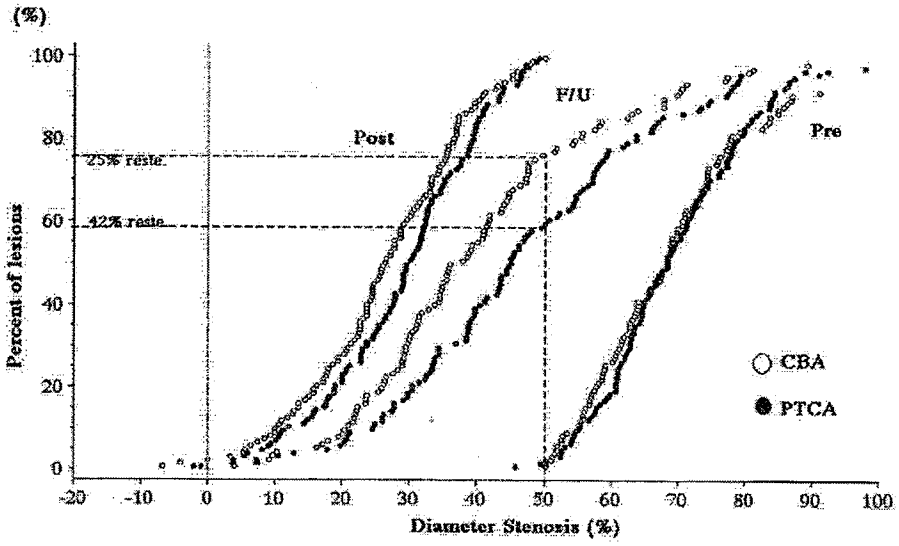
Table IV. Angiographic results

	CBA group (n = 111)	PTCA group (n = 118)	P value
Before procedure			
Reference diameter (mm)	2.17 ± 0.43	2.21 ± 0.42	.495
MLD (mm)	0.66 ± 0.31	0.68 ± 0.28	.724
%DS	69.7 ± 13.3	69.5 ± 11.3	.898
Lesion length (mm)	11.3 ± 6.6	12.7 ± 6.7	.143
After procedure			
Reference diameter (mm)	2.25 ± 0.42	2.29 ± 0.46	.490
MLD (mm)	1.65 ± 0.39	1.63 ± 0.45	.663
%DS	26.2 ± 11.7	28.9 ± 10.3	.072
Acute gain (mm)	0.99 ± 0.43	0.95 ± 0.43	.504
At follow-up			
Reference diameter (mm)	2.08 ± 0.67	2.10 ± 0.64	.802
MLD (mm)	1.31 ± 0.48	1.18 ± 0.58	.080
%DS	40.8 ± 19.2	47.5 ± 20.4	.011
Late loss (mm)	0.36 ± 0.53	0.43 ± 0.53	.280
Loss index	0.38 ± 0.76	0.47 ± 0.61	.346
Restenosis (%)			
All	25.2	41.5	.009
B1*	11.1	33.3	.023
B2*	25.5	43.6	.057
C*	42.9	48.1	.694
Reference diameter <2.25 mm	24.2	49.2	.003
Reference diameter ≥2.25 mm	26.7	33.3	.472

Acute gain defined as MLD after angioplasty minus MLD before angioplasty. Late loss is MLD after angioplasty minus MLD at follow-up angioplasty. Loss index is the average ratio of late loss to acute gain.
*ACC/AHA classification.

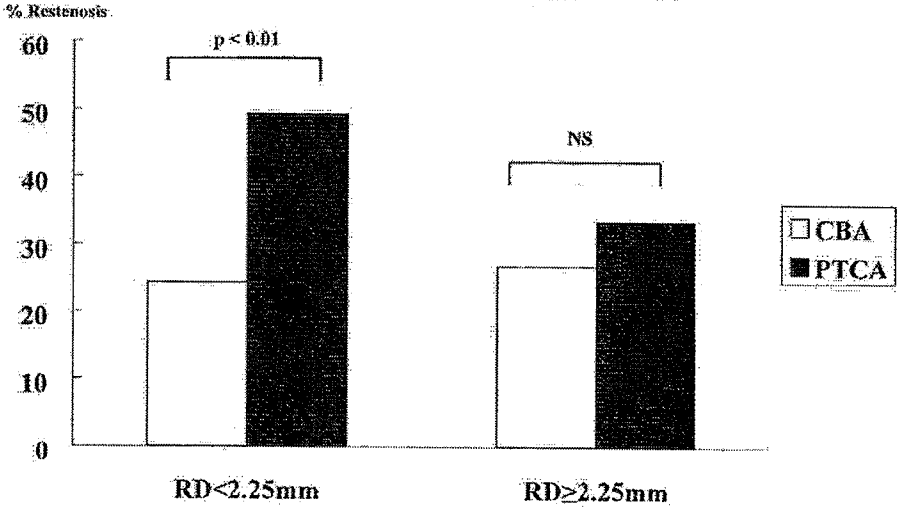
restenosis rates for CBA and PTCA were 11.1% versus 33.3% in type B1 lesions (P = .023), 25.5% versus 43.6% in type B2 lesions (P = .057), and 42.9% versus 48.1% in type C lesions (P = .694). The percentage of patients medicated with cilostazol as an antiplatelet agent was similar in both groups (CBA vs PTCA, 25.0% vs 24.5%).

Figure 2



Cumulative distribution, %DS.

Figure 3

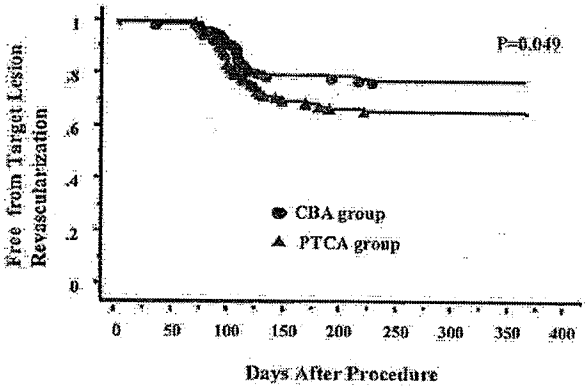


Restenosis rates, subgroup analysis.

Late clinical follow-up

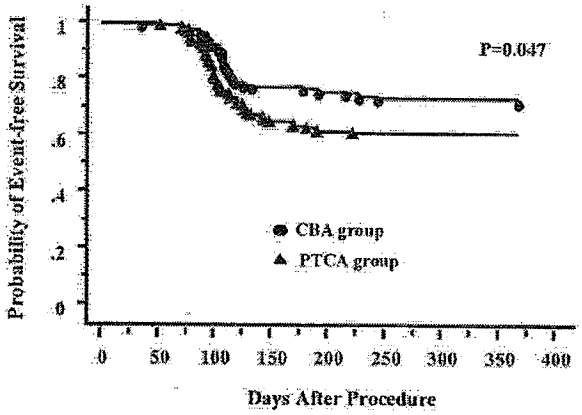
Data on all events including late cardiac events are shown in Table V. Clinical follow-up data were available for 231 of the 232 patients (99.6%). By year 1, there were 3 deaths in the CBA group (none in hospital and 3 during follow-up), for a mortality rate of 2.6%. There were 3 deaths (1 in hospital and 2 during follow-up) in the PTCA group, for a mortality rate of 2.5%. The cumulative distribution of target lesion revascularization (TLR) is shown in Figure 4. Fewer patients in the CBA group underwent TLR (22.1% vs 33.9%, $P = .049$). Event-free survival was 72.8% in the CBA group compared with 61.0% in the PTCA group ($P = .047$) (Figure 5).

Figure 4



Target lesion revascularization.

Figure 5



Event-free survival.

Discussion

Restenosis remains the major limitation of the long-term success of coronary angioplasty. The complex, vexing problem of restenosis after balloon angioplasty is influenced by a variety of clinical and anatomic factors. Vessel size is one of these important anatomic factors. The restenosis rate is inversely related to the reference vessel diameter.[19] In the Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART) of 598 patients undergoing PTCA, Hirshfeld et al[19] reported a significantly higher restenosis rate of 44% in vessels <2.9 mm compared with a restenosis rate of 34% in vessels >2.9 mm. A similar relationship between vessel size and restenosis was observed in the angioplasty arm of one stent trial[2] and in one intravascular ultrasonography study.[20] Compared with conventional balloon, stents have significantly reduced the incidence of restenosis,[2,3] but these results were obtained in selected patients with relatively large vessels (diameter ≥3.0 mm) and simple lesions. When stent indications are expanded to small vessels or complex lesions, the efficacy in long-term results is attenuated[4-13] because the treatment of in-stent restenosis (especially diffuse in-stent restenosis) remains unsatisfactory.[21,22] Because an effective device for small vessels has yet to be established, PTCA is commonly performed for such lesions. Accordingly, interventions designed to ameliorate restenosis would have a greater relative impact if applicable to small vessels.

Cutting Balloon

The hypothesis of the Cutting Balloon is that the extent of vascular injury is controlled and localized to the area of incisions and that interincisional segments are spared.[23,24] In animal experiments with the sharp surgical incisions, medial smooth muscle cells were less stretched, and the vascular injury was localized to the incision sites.[23] In addition, platelet-derived growth factor A messenger RNA expression and DNA synthesis were localized to the incisional segments after Cutting Balloon dilatation but were observed circumferentially after conventional balloon angioplasty dilatation.[24] These experiments indicate that the Cutting Balloon can minimize the traumatic vessel wall injury[25] that probably triggers a series of cellular and subcellular events leading to myointimal proliferation and consequently to restenosis.[26-28] However, the mechanism of these beneficial effects of the Cutting Balloon has not been evaluated clinically.

Clinical experience with CBA in small vessels has been reported previously.[29-31] The CBASS study (Cutting Balloon Angioplasty for Small Size Vessels)[31] showed a 26% restenosis rate at 4 months for the Cutting Balloon arm and a 48% restenosis rate for the PTCA arm when used for vessel diameter <2.6 mm. Our single-center experience showed not only similar restenosis rates but also favorable 1-year clinical results.

Table V. Cumulative 1-year clinical outcome

End point	CBA group (n = 113)	PTCA group (n = 118)	p value
Death (%)	2.6	2.5	.986
Q-wave MI (%)	0	0	—
Emergency CABG (%)	0	0	—
Target lesion revascularization (%)	22.1	33.9	.049
Target vessel revascularization (%)	24.8	36.4	.050
Any event (%)	27.2	39.0	.047

Effect of CBA on angiographic outcomes

In the current study, initial results, including acute gain, were similar between patients undergoing CBA and PTCA. However, the late loss index was less and the restenosis rate was correspondingly lower in CBA than in PTCA.[29-31] In our study, postprocedural residual DS in the CBA group tended to be lower than that in the PTCA group (26.2% ± 11.7% vs 28.9% ± 10.3%, $P = .072$). At follow-up, residual DS in the CBA group was significantly lower than that in the PTCA group (40.8% ± 19.2% vs 47.5% ± 20.4%, $P = .011$). The Cutting Balloon/artery ratio was larger in our study than that in other studies (1.25 vs 1.0-1.1). Tsukahara et al[32] reported that higher balloon/artery ratios were associated with lower residual DS, suggesting that the oversized balloon is effective. Compared with PTCA, the average balloon/artery ratio was similar (1.25 ± 0.24 vs 1.22 ± 0.19, not significant) in this study. Also, the average maximum balloon pressure and the average number of inflation times were smaller in the CBA group (6.4 ± 1.9 atm vs 8.8 ± 2.7 atm, $P < .0001$; 2.5 ± 1.5 vs 3.4 ± 3.3 times, $P = .023$). It was thought that plaque compression, one of the mechanisms in the lumen enlargement, was larger in the CBA compared with PTCA. Higher Cutting Balloon/artery ratios and multiple inflation may cause more arterial damage compared with other studies, but the CBA group provided superior angiographic outcomes at follow-up than the PTCA group (restenosis rate 25.2% vs 41.5%, $P = .009$). Although the study was not powered for subgroup analysis, the Cutting Balloon seemed to provide the most benefit for outcomes in type B1 and B2 lesions. More important, in group 1 (reference vessel <2.25 mm), the incidence of restenosis in the Cutting Balloon group was significantly lower than that in the PTCA group (24.2% vs 49.2%, $P = .003$).

Clinical benefit of CBA

The target lesion revascularization rate at year 1 was significantly lower in the CBA group compared with the PTCA group (22.1% vs 33.9%, $P = .049$). The target vessel revascularization rate tended to be lower in the CBA group compared with the PTCA group (24.8% vs 36.4%, $P = .050$). These clinical results were consistent with the angiographic results. Our study suggests that CBA provides superior clinical outcomes compared with PTCA. CBA is considered to be an effective strategy in small coronary arteries.

Study limitation

Although this was a prospective, randomized study, the number of patients enrolled was only 248 and the study represents a single-center experience. Additionally, a third arm where patients were randomized to stenting would have been desirable because of the increasing popularity of stenting for all types of lesions. At the beginning of our study, stenting was not well established in small vessels and conventional balloon was still the routine form of treatment. Furthermore, recent studies have suggested that stenting in small vessels does not improve early and late outcomes compared with PTCA.[33,34]

Also, the definition of small vessel may have had an impact with intravascular ultrasonography; however, other small vessel studies by Ergene et al[16] and Kastrati et al[34] used only angiographic analysis.

Also in our study, heavily calcified lesions and lesions on a bend were excluded from the enrollment. The Cutting Balloon may have difficulty accessing or crossing angulated and calcified lesions because we had 8 delivery failures in our study. Although no selection bias was intentionally used, there were slightly more angulated lesions in the PTCA group than in the CBA group (19% vs 9%). Finally, angiographic follow-up analysis in our study was 3 months versus the standard 6 months normally used in other studies. However, Nobuyoshi et al[35] reported that stenosis diameter decreased markedly between 1 month and 3 months after angioplasty and reached a plateau thereafter. Because our study was a comparison between CBA and PTCA, we decided to conduct a 90-day angiographic follow-up. Also, it should be noted that in another study at our institution with the Cutting Balloon angiographic results at 3 months were similar to those at 6 months.

Conclusion

This study suggests that CBA provides superior angiographic and clinical outcomes compared with PTCA in small coronary arteries. Cutting Balloon angiplasty is thought to be an effective strategy for the treatment of small coronary arteries.

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